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Efficient Synthesis of α-Ketoamides via 2-Acyl-5-aminooxazoles by Reacting Acyl Chlorides and α-Isocyanoacetamides

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ABSTRACT

Acyl chlorides and α-isocyanoacetamides undergo an efficient reaction in dichloromethane in the presence of triethylamine to give 2-acyl-5-aminooxazoles. Subsequent acid hydrolysis of the 5-aminooxazole moiety leads to α-ketoamides in good overall yields.

α-Ketoamides[1] represent a privileged scaffold in medicinal chemistry, and this structural motif can be found in natural products such as the immunosuppressant drugs FK-506 and rapamycin.[2] In addition, α-ketoamides are used as serine or cysteine protease inhibitors;[3] the higher electrophilicity of the α-keto group makes the inhibition of proteases possible, thanks to the formation of a covalent hemiketal or hemithioketal adduct with the -OH or -SH group of serine or cysteine protease, respectively.

For these reasons, a vast array of synthetic procedures for the preparation of α-ketoamides have been developed over the past decades.[4] Among these methodologies, the use of isocyanides as reacting partner to generate α-ketoamides dates back to 1961, when Ugi reported that α-ketoimidoyl chlorides (**3**), obtained by condensation between acyl chlorides (**1**) and isocyanides (**2**), could be converted upon hydrolysis into α-ketoamides (**4**) (Scheme 1).[5]

Further syntheses of α-ketoamides using isocyanides were encouraged by a renewed interest in this synthon as a pivotal

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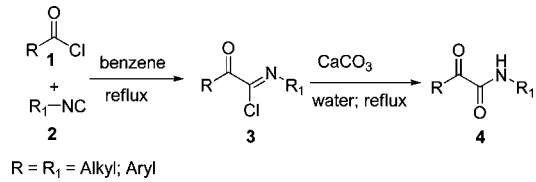
Scheme 1. Formation of α-Ketoimidoyl Chloride and Its Subsequent Hydrolysis



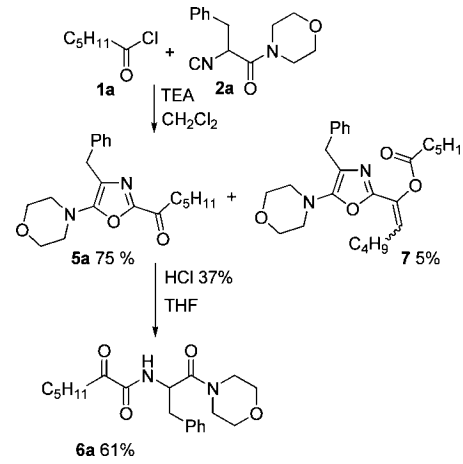
substrate in multicomponent reactions, and in recent years novel synthetic strategies exploiting the isocyanides emerged from the literature.[6] Despite these new methodologies, the coupling between acyl chlorides and isocyanides to generate α-ketoamides remains the most practical transformation. Nevertheless, formation and hydrolysis of the key intermediate α-ketoimidoyl chloride are known to be problematic, requiring several hours of heating.[4b] Even though the use of microwave conditions has reduced the reaction time,[7] this methodology is impaired by low yields and harsh experimental conditions that are not always compatible with functionalized substrates. In light of this, a general and straighforward methodology to rapidly prepare structurally diverse α-ketoamides is still demanded.

In connection with our ongoing study on the reactivity of α-isocyanoacetamides,[8] we report herein their reaction with acyl chlorides as a novel and reliable methodology to provide access to α-ketoamides.

With the use of hexanoyl chloride **1a** and α-isocyanoacetamide **2a** as test substrates, 2-acyl-5-aminooxazole **5a**[9] was isolated in very good yields, which upon acid hydrolysis led to the α-ketoamide **6a** in 61% yield (Scheme 2).

The following optimized experimental procedure was used: A solution of acyl chloride **1a** (1 equiv) in dichloromethane

Scheme 2. Synthesis of 2-Acyl-5-aminooxazole **5a** and Its Subsequent Acid Hydrolysis to α-Ketoamides **6a**

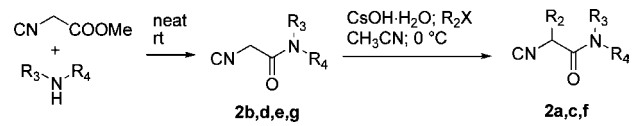


was added dropwise to a mixture of α-isocyanoacetamide **2a** (1 equiv) and TEA (1 equiv) in dichloromethane under a nitrogen atmosphere. The reaction was stirred at room temperature for 1 h. After workup and column chromatography, the 2-acyl-5-aminooxazole **5a** was dissolved in THF, and HCl 37% (100 μL/0.100 mmol) was added dropwise at 0 °C.[10] The reaction was stirred at room temperature for 1 h, worked up, and purified by column cromatography to give the α-ketoamide **6a**.

2-Acyl-5-aminooxazole **5a** came with the formation of the enol ester byproduct **7** (as a single geometrical isomer), due to the reaction of the enolate ion with a second molecule of acyl chloride (Scheme 2). Up to 45% yield of **7** was isolated when the reaction was carried out in toluene under otherwise identical conditions. However, by performing the reaction in dichloromethane and by adding dropwise a solution of acyl chloride in dichloromethane, the formation of **7** was reduced to a minimum with concurrent increase in the yield of the desired 2-acyl-5-aminooxazole.

The generality of this novel transformation was demonstrated by applying the procedure to various acyl chlorides and α-isocyanoacetamides. The α-isocyanoacetamides **2b,d,e,g** were prepared by solventless aminolysis of methyl isocyanoacetate with a primary or secondary amine as reported by Dömling,[11] and the subsequent alkylation in the presence of cesium hydroxide[12] gave rise to the α-substituted α-isocyanoacetamides **2a,c,f** (Scheme 3).

Scheme 3. Synthesis of α-Isocyanoacetamides Building Blocks



Five commercially available acyl chlorides, **1a**−**e**, and seven easily accessible α-isocyanoacetamides, **2a**−**g**, were used as starting materials (Figure 1).

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(7) Chen, J. J.; Deshpande, S. V. *Tetrahedron Lett.* **2003**, *44*, 8873–8876.

(8) Selected examples: (a) Zhao, G.; Sun, X.; Bienaymè, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700–6701. (b) Janvier, P.; Bois-Choussy, M.; Bienaymè, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 811–814. (c) Tron, G. C.; Zhu, J. *Synlett* **2005**, 532–534. (d) Bonne, D.; Dekhane, M.; Zhu, J. *Org. Lett.* **2005**, *7*, 5285–5288. (e) Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2006**, *8*, 4145–4148. (f) Bughin, C.; Zhao, G.; Bienaymè, H.; Zhu, J. *Chem.—Eur. J.* **2006**, *12*, 1174–1184. (g) Wang, S.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Eur. J. Org. Chem.* **2007**, *407*, 6–4080. (h) Pirali, T.; Tron, G. C.; Masson, G.; Zhu, J. *Org. Lett.* **2007**, *9*, 5275–5278.

(9) Other oxazoles syntheses starting from isocyanides and acyl chlorides are described in literature. See for example: (a) Suzuki, M.; Iwasaki, T.; Matsumoto, K.; Okumura, K. *Synth. Commun.* **1972**, *2*, 237–242. (b) Schröder, R.; Schöllkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533–546. (c) Huang, W.-S.; Zhang, Y.-X.; Yuan, C.-Y. *Synth. Commun.* **1996**, *26*, 1149–1154. (d) dos Santos, A.; El Kaúm, L.; Grimaud, L.; Ronserray, C. *Chem. Commun.* **2009**, 3907–3909. (e) El Kaúm, L.; Grimaud, L.; Schiltz, A. *Tetrahedron Lett.* **2009**, *50*, 5235–5237.

(10) Better yields were obtained by using 37% HCl (1 h, 61% for **6a**), instead of trifluoroacetic acid (32 h, 55% for **6a**).

(11) Dömling, A.; Beck, B.; Fuchs, T.; Yazback, A. *J. Comb. Chem.* **2006**, *8*, 872–880.

(12) Housseman, C.; Zhu, J. *Synlett* **2006**, *11*, 1777–1779.

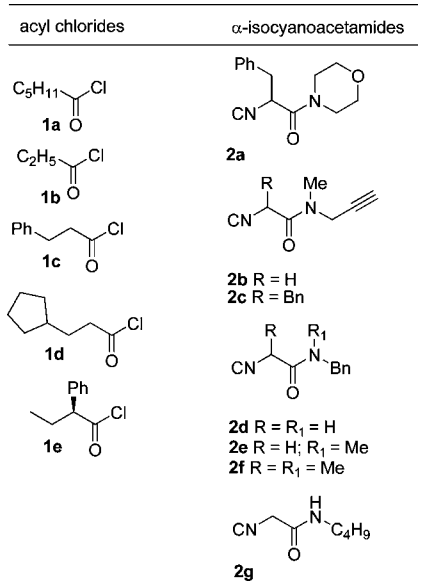


Figure 1. Structures of acyl chlorides and α-isocyanoacetamides.

The 2-acyl-5-aminooxazoles **5a**−**l** were obtained in good to excellent yields (Figure 2). Subsequent hydrolysis of these

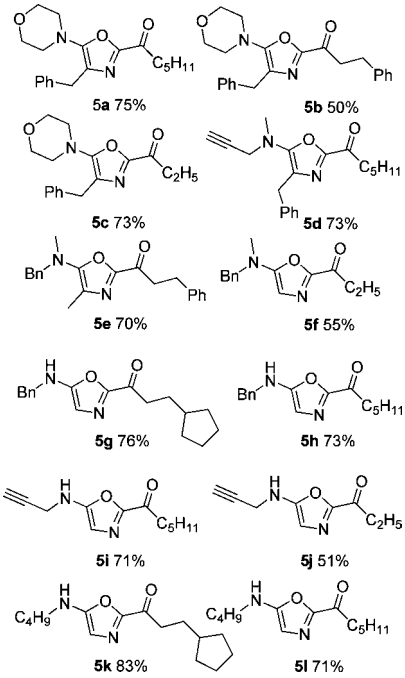


Figure 2. Synthesized 2-acyl-5-aminooxazoles.

intermediates gave the α-ketoamides **6a**−**l** listed in Figure 3 in good yields.

Structural modifications of both components do not affect the yield of the corresponding reactions, which are still characterized by good overall efficiency. Aliphatic acyl chlorides were found to be good substrates, whereas

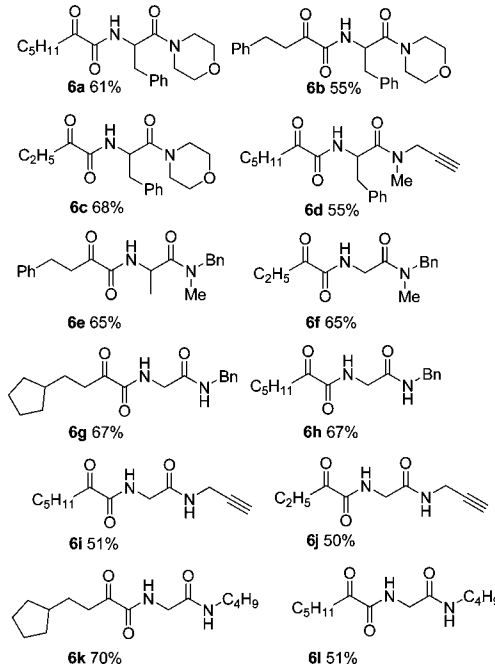
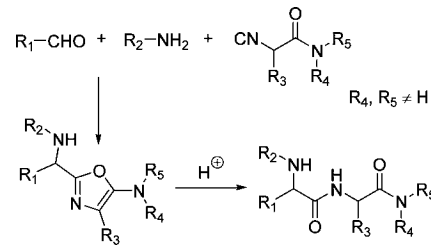


Figure 3. Synthesized α-ketoamides. The yields refer to the hydrolysis of compounds **5a**−**l**.

α-branched acyl chloride **1e** afforded the oxazole in lower yields. Both α-unsubstituted and α-substituted α-isocyanoacetamides participated in the reaction. It is remarkable that, compared to the multicomponent reaction between aldehydes, amines, and isocyanoacetamides,[13] which leads to the formation of a 5-aminooxazole and, after acid hydrolysis, to a dipeptidic structure (Scheme 4), this new strategy works

Scheme 4. Previously Reported 3-CR between Aldehydes, Amines, and α-Isocyanoacetamides[13]



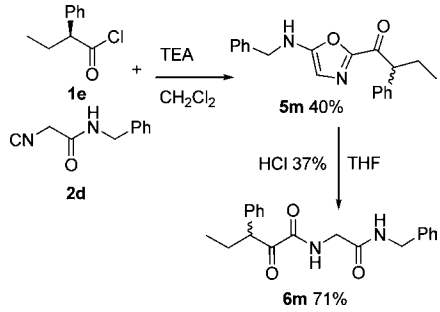
well not only with tertiary α-isocyanoacetamides but also with secondary ones (**2d,g**), leading to a marked peptidomimetic scaffold. The reason for this result can be tentatively explained by assuming an increase in stability of the aminooxazoles due to the presence of the electron-withdrawing acyl group at the 2 position.

From a mechanistic point of view, the reaction between acyl chloride and α-isocyanoacetamide might pass through

(13) (a) Sun, X.; Janvier, P.; Zhao, G.; Bienaymé, H.; Zhu, J. *Org. Lett.* **2001**, *3*, 877–880. (b) Janvier, P.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567.

the ketene intermediate or via direct α-addition of the isocyanide to the acyl chloride to give the α-ketoimidoyl chloride. We therefore investigated the reaction starting from the optically active (*S*)-2-phenylbutanoyl chloride (**1e**), checking the stereochemistry of the product **5m** by ^{1}H NMR in the presence of the chiral reagent Eu(tfc)$_3$. A racemic mixture was detected, suggesting that the reaction proceeds through a ketene intermediate (Scheme 5).

Scheme 5. Reaction with (*S*)-2-Phenylbutanoyl Chloride

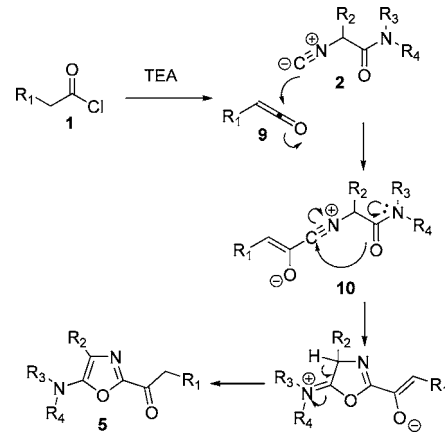


This conclusion is in accord with our experimental observations. By reacting acyl chlorides and α-isocyanoacetamides without TEA, only the α-ketoimidoyl chloride was formed; this intermediate could not be transformed to the corresponding 2-acyl-5-aminooxazole as addition of the base gave rise to a complex mixture. Moreover, when performing the reaction between benzoyl chloride and **2d** in the presence of TEA at room temperature, only starting materials were recovered.

A plausible reaction scenario is depicted in Scheme 6. Acyl chloride **1** reacts with TEA forming the corresponding ketene **9**. The isocyanide **2** attacks the electrophilic carbon atom to produce the nitrilium ion **10**. This latter intermediate cyclizes and, after proton transfer, gives the 2-acyl-5-aminooxazole **5**.

In conclusion, we documented a very straightforward two-step synthesis of α-ketoamides starting from acyl chlorides

Scheme 6. Proposed Mechanism for the Synthesis of 2-Acyl-5-aminooxazoles



and α-isocyanoacetamides, two easily accessible starting materials. This synthesis has clear advantages over the previously reported methodologies: the entire sequence is realized under mild and simple conditions. Besides efficiency, the overall sequence displays versatility, providing α-ketoamides with four potential points of diversity.

We believe that the synthesis reported herein can find application in a number of fields in view of the medicinal importance of this scaffold.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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