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# Expedient Synthesis of a 72-Membered Isoxazolino-β-ketoamide Library by a 2·3-Component Reaction

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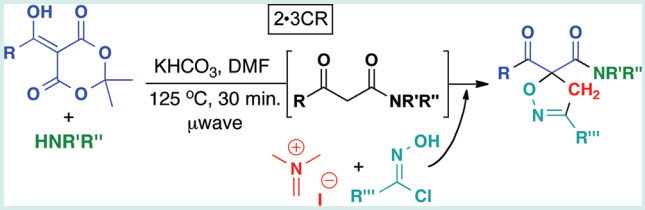
Supporting Information

**ABSTRACT:** An efficient 2·3-component reaction (2·3CR; a 2-component reaction followed, in one pot, by a 3-component reaction) is presented for the synthesis of isoxazolino-β-ketoamides. This 2·3CR proceeds by (i) a Meldrum's acid-generated acyl ketene, which is trapped by an amine to form a β-ketoamide intermediate in a 2CR followed, in one pot, by (ii) a Mannich reaction followed by elimination of dimethyl amine·HCl to generate an α,β-unsaturated β-ketoamide dipolarophile that reacts in a nitrile oxide 1,3-dipolar cycloaddition reaction. This one-pot 2·3CR process delivers the targeted isoxazolino-β-ketoamide product. A total of 72 compounds are presented, all of which have been submitted to the *NIH Molecular Libraries Small Molecule Repository* for high-throughput biological screening.




**KEYWORDS:** *2·3-component reaction, isoxazolino-β-ketoamides, one pot, isoxazolino-β-ketoamide product*

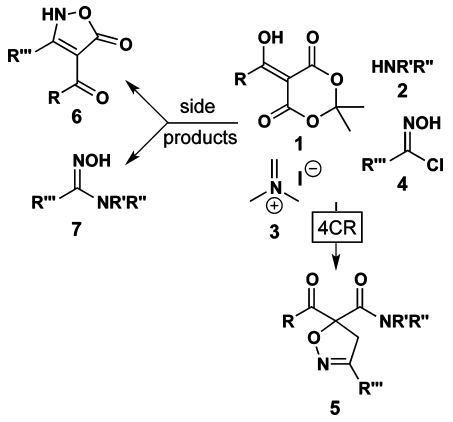
Multicomponent reactions offer an expedient route to complex targets[1] since the combination of three or more reactants within a single reaction typically leads to a shorter reaction sequence and fewer purification steps.[1] Moreover, multicomponent products are comparatively far more elaborate than their starting material counterparts and, by altering a single reactive component, a wide range of diversity can be achieved. For these reasons, multicomponent reactions, such as the Biginelli,[2] Passerni,[3] Hantzche,[4] and Ugi[5] reactions, have been widely used for the construction of combinatorial libraries.[6] The development of new multicomponent reactions has broad implications in synthetic methodology, library production, and biological screening.

Isoxazolines have little precedence as pharmacophores. However, we have discovered that a class of isoxazolines function as a cystic fibrosis transmembrane conductance regulator protein activator[7] and others have previously shown this substructure to be bioactive in various other systems.[8] As an under exploited heterocycle, isoxazolines could potentially find various new applications and serve as future synthetic targets. To address this possibility, expedient library synthesis is needed to enable the requisite random screening.

Isoxazolines are synthons for β-amino acids[9] and γ-amino alcohols,[10] which are abundant in natural products and medicinal compounds.[11] Consequently, the diversity oriented synthesis of isoxazolines can have considerable significance. To this end, we present here the synthesis of a seventy-two membered library of isoxazolino-β-ketoamides prepared by a modified multicomponent reaction with the ability for easy diversification.

We recently reported a 4-component reaction (4CR) for the synthesis of isoxazolino-β-ketoamides[12] as outlined in Scheme 1.

**Scheme 1. 4CR Route to Isoxazolino-β-ketoamides**




This initial investigation was conducted as a proof-of-concept study for the development of a multicomponent macrocylization reaction, which we have now evolved into a general protocol for the synthesis isoxazolino-β-ketoamides. This procedure incorporates an acyl ketene precursor (**1**) and an amine (**2**) to form the β-ketoamide moiety, which then undergoes a Mannich reaction with Eschenmoser's salt (**3**) followed by elimination of dimethyl ammonium chloride. The

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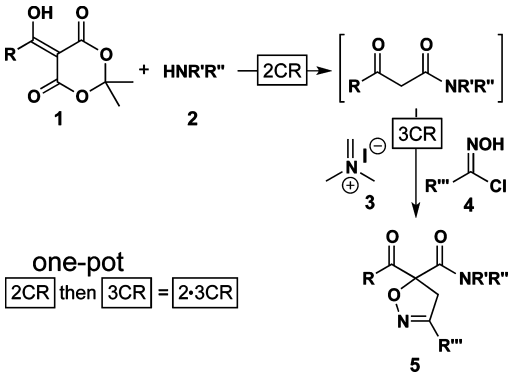
resulting doubly activated Michael acceptor then serves as a dipolarophile in a nitrile oxide cycloaddition (⇒ **4**) to, in one-pot, deliver the isoxazolino-*β*-ketoamide target (**5**). Our previously reported yields for this 4CR reaction ranged from 39 to 50%. Herein, we demonstrate modification and expansion of this versatile transformation.

The combination of four reactants can lead to undesirable side-product formation and, consequently, lower isoxazolino-*β*-ketoamide yields. Despite these inherent limitations, our 4CR produces modest yields (39−50%) of the targeted product because of the high reactivity of the acyl ketene with the amine nucleophile. This high acyl ketene/amine reactivity effectively suppresses side reactions that form isoxazol-5(2*H*)-ones (**6**) and *N*-hydroxyimidamides (**7**). That said, we report here a modified method that delivers isoxazolino-*β*-ketoamides in both higher average yields and cleaner reactions, advancements that enable efficient library synthesis.

**Scheme 2. Isoxazolino-*β*-ketoamides by a Multicomponent (2·3CR) Process**




As delineated in Scheme 2, performing the multicomponent reaction as a 2·3CR (a 2-component reaction followed by a 3-component reaction), instead of a 4CR, results in isoxazolino-*β*-ketoamide yields up to 88% as well as excellent product purity. This 2·3CR was accomplished as a one-pot procedure by heating a DMF solution of the acyl ketene precursor in the presence of only the amine nucleophile, thus preforming the *β*-ketoamide in a 2CR. While it is known that dioxolinones and Meldrum's acids fragment thermally to acyl ketenes, it must be said that an alternative mechanism where the amine attacks first, followed by loss of $CO_2$ and acetone, is possible. Subsequent addition of Eschenmoser's salt and chlorooxime reagents, to the same flask, results in a 3CR (collectively, a 2·3CR) that delivers the isoxazolino-*β*-ketoamide product. This 2·3CR modification essentially avoids both the chlorooxime + acyl ketene cycloaddition side reaction (→ isoxazol-5(2*H*)-ones; **6**; Scheme 1) and the amine + chlorooxime side reaction (→ *N*-hydroxyimidamides; **7**; Scheme 1), while proficiently effecting the desired transformation (→ isoxazolino-*β*-ketoamide; **5**; Scheme 2).

In addition to the 2·3CR synthetic modification, we wanted to expand the scope of this reaction by utilizing an array of diverse reactants (Figure 1). A total of eight amines were used. Both aliphatic and aromatic amines worked well; however, yields dropped when aminothiazole, ethanolamine, or acetohydrazide where used. For the library reported here, three different acyl ketene precursors (*p*-methoxyphenyl,[13] cyclopropyl,[14] and methyl) as well as three different chlorooximes (*o*-pyridinyl,[15] *o*-trifluoromethylphenyl,[16] and carboethoxy[17]) were used. We also demonstrate that these substituted acyl ketenes and chlorooximes tolerate the 2·3CR reaction conditions. Isolated yields for all variations are shown in Table 1.

Considerable functional group diversity is represented in this library in which product molecular weights range from 272 to 496. Manipulation of the acyl ketene-, amine-, and chlorooxime-derived R-groups allow for dramatic alteration of the isoxazolino-*β*-ketoamide three-dimensional shape. Together, the ease of altering functional groups, molecular weights, and molecular geometry with this 2·3CR-based methodology allows for the rapid assembly of a library of biological relevant isoxazolino-*β*-ketoamides.

We have successfully synthesized a library of seventy-two isoxazolino-*β*-ketoamides with novel 2·3CR-based methodology. This library effectively expands the scope of our multicomponent methodology and demonstrates its application in diversity-oriented synthesis. Compared to its 4CR variant, this one-pot 2·3CR method delivers the targeted scaffold with much improved yields − as much as 38% in side-by-side comparative reactions. The compounds reported here have been deposited in the *NIH Molecular Libraries Small Molecule Repository* for high-throughput biological screening and assay results for these molecules and similar analogs will likely follow.

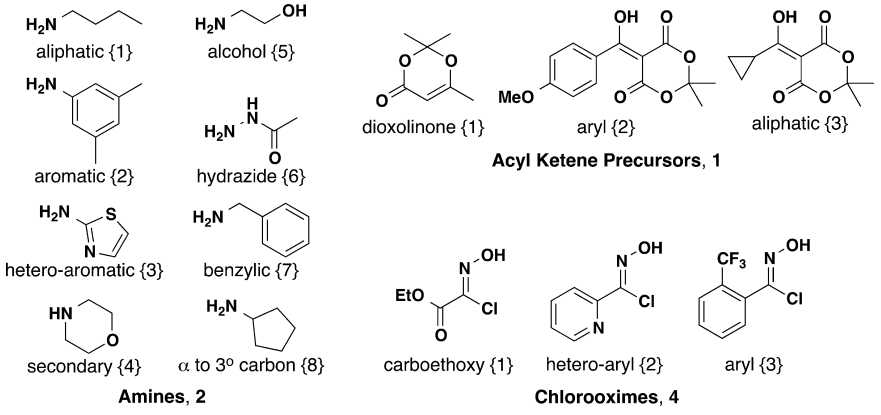



**Figure 1.** 2·3CR diversity inputs.


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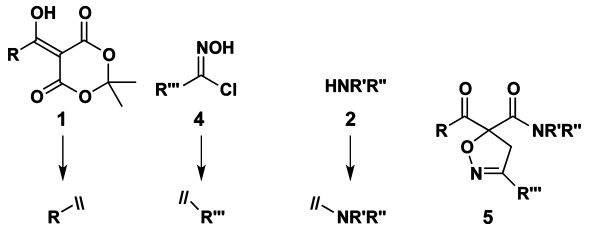
Table 1. Library of Isoxazolino-$\beta$-ketoamides




| entry | acyl ketene | chloro-oxime | amine | product | yield (%) |
|---|---|---|---|---|---|
| 1 | {1} | {1} | {1} | 5{1,1,1} | 80 |
| 2 | {1} | {1} | {2} | 5{1,1,2} | 79 |
| 3 | {1} | {1} | {3} | 5{1,1,3} | 30 |
| 4 | {1} | {1} | {4} | 5{1,1,4} | 40 |
| 5 | {1} | {1} | {5} | 5{1,1,5} | 40 |
| 6 | {1} | {1} | {6} | 5{1,1,6} | 51 |
| 7 | {1} | {1} | {7} | 5{1,1,7} | 76 |
| 8 | {1} | {1} | {8} | 5{1,1,8} | 88 |
| 9 | {1} | {2} | {1} | 5{1,2,1} | 75 |
| 10 | {1} | {2} | {2} | 5{1,2,2} | 76 |
| 11 | {1} | {2} | {3} | 5{1,2,3} | 31 |
| 12 | {1} | {2} | {4} | 5{1,2,4} | 44 |
| 13 | {1} | {2} | {5} | 5{1,2,5} | 31 |
| 14 | {1} | {2} | {6} | 5{1,2,6} | 50 |
| 15 | {1} | {2} | {7} | 5{1,2,7} | 78 |
| 16 | {1} | {2} | {8} | 5{1,2,8} | 83 |
| 17 | {1} | {3} | {1} | 5{1,3,1} | 81 |
| 18 | {1} | {3} | {2} | 5{1,3,2} | 80 |
| 19 | {1} | {3} | {3} | 5{1,3,3} | 19 |
| 20 | {1} | {3} | {4} | 5{1,3,4} | 48 |
| 21 | {1} | {3} | {5} | 5{1,3,5} | 41 |
| 22 | {1} | {3} | {6} | 5{1,3,6} | 38 |
| 23 | {1} | {3} | {7} | 5{1,3,7} | 75 |
| 24 | {1} | {3} | {8} | 5{1,3,8} | 75 |
| 25 | {2} | {1} | {1} | 5{2,1,1} | 30 |
| 26 | {2} | {1} | {2} | 5{2,1,2} | 50 |
| 27 | {2} | {1} | {3} | 5{2,1,3} | 8 |
| 28 | {2} | {1} | {4} | 5{2,1,4} | 15 |
| 29 | {2} | {1} | {5} | 5{2,1,5} | 35 |
| 30 | {2} | {1} | {6} | 5{2,1,6} | 44 |
| 31 | {2} | {1} | {7} | 5{2,1,7} | 55 |
| 32 | {2} | {1} | {8} | 5{2,1,8} | 64 |
| 33 | {2} | {2} | {1} | 5{2,2,1} | 60 |
| 34 | {2} | {2} | {2} | 5{2,2,2} | 58 |
| 35 | {2} | {2} | {3} | 5{2,2,3} | 17 |
| 36 | {2} | {2} | {4} | 5{2,2,4} | 31 |
| 37 | {2} | {2} | {5} | 5{2,2,5} | 30 |
| 38 | {2} | {2} | {6} | 5{2,2,6} | 33 |
| 39 | {2} | {2} | {7} | 5{2,2,7} | 60 |
| 40 | {2} | {2} | {8} | 5{2,2,8} | 60 |
| 41 | {2} | {3} | {1} | 5{2,3,1} | 62 |
| 42 | {2} | {3} | {2} | 5{2,3,2} | 42 |
| 43 | {2} | {3} | {3} | 5{2,3,3} | 12 |
| 44 | {2} | {3} | {4} | 5{2,3,4} | 46 |
| 45 | {2} | {3} | {5} | 5{2,3,5} | 60 |
| 46 | {2} | {3} | {6} | 5{2,3,6} | 45 |
| 47 | {2} | {3} | {7} | 5{2,3,7} | 70 |
| 48 | {2} | {3} | {8} | 5{2,3,8} | 68 |
| 49 | {3} | {1} | {1} | 5{3,1,1} | 49 |
| 50 | {3} | {1} | {2} | 5{3,1,2} | 78 |
| 51 | {3} | {1} | {3} | 5{3,1,3} | 23 |
| 52 | {3} | {1} | {4} | 5{3,1,4} | 31 |
| 53 | {3} | {1} | {5} | 5{3,1,5} | 37 |
| 54 | {3} | {1} | {6} | 5{3,1,6} | 44 |
| 55 | {3} | {1} | {7} | 5{3,1,7} | 52 |
| 56 | {3} | {1} | {8} | 5{3,1,8} | 62 |
| 57 | {3} | {2} | {1} | 5{3,2,1} | 77 |
| 58 | {3} | {2} | {2} | 5{3,2,2} | 70 |
| 59 | {3} | {2} | {3} | 5{3,2,3} | 18 |
| 60 | {3} | {2} | {4} | 5{3,2,4} | 39 |
| 61 | {3} | {2} | {5} | 5{3,2,5} | 35 |
| 62 | {3} | {2} | {6} | 5{3,2,6} | 43 |
| 63 | {3} | {2} | {7} | 5{3,2,7} | 54 |
| 64 | {3} | {2} | {8} | 5{3,2,8} | 62 |
| 65 | {3} | {3} | {1} | 5{3,3,1} | 76 |
| 66 | {3} | {3} | {2} | 5{3,3,2} | 62 |
| 67 | {3} | {3} | {3} | 5{3,3,3} | 9 |
| 68 | {3} | {3} | {4} | 5{3,3,4} | 34 |
| 69 | {3} | {3} | {5} | 5{3,3,5} | 69 |
| 70 | {3} | {3} | {6} | 5{3,3,6} | 32 |
| 71 | {3} | {3} | {7} | 5{3,3,7} | 63 |
| 72 | {3} | {3} | {8} | 5{3,3,8} | 40 |

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, characterization data, and $^{1}H$ and $^{13}C$ NMR spectra of 20 representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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