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Bioactive 2-Oxazolines: A New Approach via One-Pot, Four-Component Reaction

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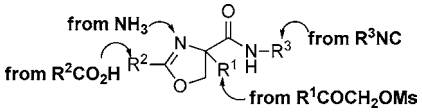
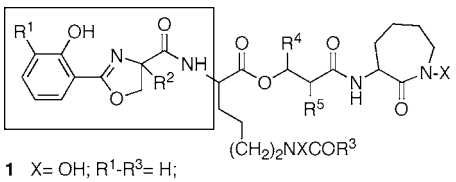
ABSTRACT



Substituted 2-oxazolines of the general structure shown above are found in several families of bioactive natural products and can be prepared in an efficient and general one-pot, four-component condensation.

Oxazolines are widely used in polymer chemistry as synthetic reagents and most recently as ligands in asymmetric synthesis.[1] Alkyl- and aryl-substituted 2-oxazolines are also present in marine natural products[2] and are important pharmacophores in numerous bioactive natural products that display cytotoxic, antitumor, neuroprotective, antibiotic, or antifungal properties.

Some representative examples (Figure 1) include the cytotoxic agent brasilibactin **1**,[3] a family of five antitumor



1 X= OH; R^1-R^3= H; R^4,R^5 = CH_3 *brasilibactin A*
2 X= OH; R^2, R^4, R^5= CH_3; R^3= *n*-$C_{12}H_{25}$; R^1 = H (*BE-32030A*) or R^1= OH (*BE-32030D*)
3 X= H; R^1, R^5= H; R^2, R^4= CH_3; R^3= *cis* -CH=CH-$(CH_2)_{16}CH_3$ *didehydroxymycobactin*

Figure 1. Substituted 2-oxazolines in bioactive natural products.

substances represented by B32030A **2** and B32030B **3**,[4] and the recently discovered T-cell antigen didehydroxymycobactin **3**, a complex lipopeptide related to the mycobactin family of mammalian siderophores that utilize the 2-hydroxyphenyloxazoline carboxamide substructure (box) to sequester iron in macrophages.[5]

We have been interested in developing convergent synthetic routes to such complex oxazolines utilizing a multicomponent reaction (MCR) to assemble the key heterocyclic pharmacophore in a single flask. Here, we report a powerful and versatile 4-component condensation that efficiently produces 2-substituted oxazoline-4-carboxamides and their congeners as highlighted in **1**−**3** in good yields.

The approach we envisioned was based on the known biosynthesis of many peptide-derived oxazolines, which usually involves cyclization of *N*-acyl serine residues. We initially considered an Ugi reaction using α-diazoketones (readily prepared from acid chlorides using CH_2N_2) in place of simple aldehydes or ketones. However, mixtures of α-diazoketones, amines, isonitriles, and carboxylic acids proved unreactive, even when heated to 60−70 °C.

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(3) Tsuda, M.; Yamakawa, M.; Oka, S.; Tanaka, Y.; Hoshino, Y.; Mikami, Y.; Sato, A.; Fujiwara, H.; Ohizumi, Y.; Kobayashi, J. *J. Nat. Prod.* **2005**, *68*, 462.
(4) Tsukamoto, M.; Murooka, K.; Nakajima, S.; Abe, S.; Suzuki, H.; Hirano, K.; Kondo, H.; Kojiri, K.; Suda, H. *J. Antibiot.* **1997**, *50*, 815.
(5) Moody, D. B.; Young, D. C.; Cheng, T.-Y.; Rosat, J.-P.; Roura-mir, C.; O'Connor, P. B.; Zajonc, D. M.; Walz, A.; Miller, M. J.; Levery, S. B.; Wilson, I. A.; Costello, C. E.; Brenner, M. B. *Science* **2004**, *303*, 527.

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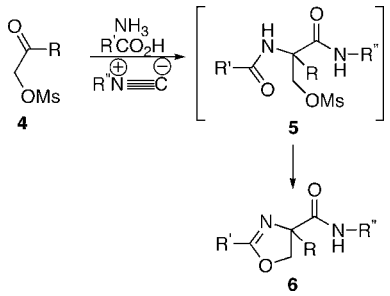
We therefore investigated Ugi condensations of the corresponding (and much more electrophilic) β-ketomesylates **4** (Scheme 1), which are readily available by the known

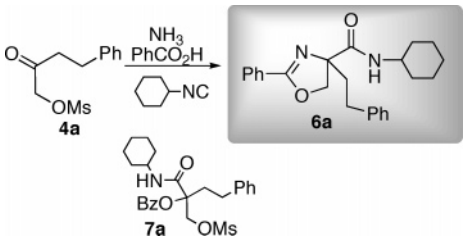
Scheme 1. Proposed MCR Approach to Substituted 2-Oxazolines



insertion reaction[6] of diazoketones with CH_3SO_3H. Our expectation was that if imine formation at the carbonyl group in **4** using ammonia were faster than displacement of the mesylate, then the intermediate diamide **5** might spontaneously cyclize in situ to the desired oxazoline **6**.

Using the β-ketomesylate **4a** (Scheme 2) as a test case, a solution of **4a** in CH_3OH was stirred with NH_3 and benzoic

Scheme 2. One-Pot Synthesis of 2-Oxazolines



acid (1 equiv each) for 30 min at 0 °C. After adding cyclohexylisonitrile (1.1 equiv) then stirring at rt for 24 h, solvent evaporation led directly to roughly equal quantities of the target oxazoline **6a** together with the corresponding three-component Passerini product **7a**.

Increasing the quantities of ammonia and benzoic acid slightly improved the yield of **6a** but did not suppress formation of **7a**. A more dramatic improvement was achieved by replacing methanol as solvent with 2,2,2-trifluoroethanol, which has been shown to improve Ugi reactions involving ammonia.[7] Under optimal conditions (4 equiv each of NH_3, $PhCO_2H$), **6a** was obtained in 61% yield (mp 89 °C) accompanied by ca. 5% of **7a**. Interestingly, no products derived from simple nucleophilic substitution of the mesylate group in **4a** were observed.

Figure 2 shows the X-ray crystal structure of **6a**, which confirmed the presence of the 2,4,4-trisubstituted oxazoline ring.

(6) Nogrady, T.; Doyle, T. W.; Morris, L. *J. Med. Chem.* **1965**, *8*, 656.
(7) Kazmaier, U.; Hebach, C. *Synlett* **2003**, 1591.

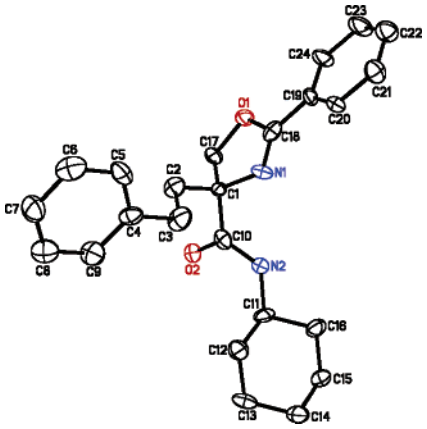


Figure 2. ORTEP diagram of the X-ray crystal structure of oxazoline **6a**. Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (deg): N(1)−C(18) = 1.270(3), O(1)−C(18) = 1.369(3), C(1)−N(1) = 1.474(3), O(1)−C(17) = 1.444(3); N(1)−C(1)−C(17) = 104.45(18), N(1)−C(18)−O(1) = 118.5(2), C(18)−O(1)−C(17) = 105.55(18), C(10)−C(1)−C(17) = 110.7(2), C(10)−C(1)−C(2) = 106.70(19).

Several examples of trisubstituted 2-oxazolines prepared by this four-component condensation illustrate the scope and generality of the method (Table 1). Precondensing the

Table 1. Synthesis of 2-Oxazolines **6** from Ketomesylates **4**

ketomesylate **4a**−**e**	R′CO_2H R′ =	R″NC R″ =	product (% yield)
4a, R = Ph$(CH_2)_2$	C_6H_5	cyclohexyl	**6a** (61)
	CH_3	cyclohexyl	**6b** (71)
	CH_3	*tert*-butyl	**6c** (73)
	Boc-(*S*)-Phe	cyclohexyl	**6d** (64)[a]
4b, R = *n*-C_7H_{15}[b]	*i*-C_3H_7	CH_2CO_2Et	**6e** (60)
	CH_3	*tert*-butyl	**6f** (80)
	Cbz-Gly	*tert*-butyl	**6g** (38)
4c, R = cyclohexyl	CH_3	CH_2CO_2Et	**6h** (63)
	i-C_3H_7	*tert*-butyl	**6i** (60)
4d, R = Ph[b]	CH_3	*tert*-butyl	**6j** (63)
4e, R = CH_3[c]	CH_3	*tert*-butyl	**6k** (60)
	C_6H_5	CH_2CO_2Et	**6l** (68)
	o-(OH)C_6H_4	*tert*-butyl	**6m** (58)[d]
	o-(OH)C_6H_4	CH_2CO_2Et	**6n** (63)[d,e]

[a] Obtained as a mixture of diastereomers. [b] Cho, B. T.; Yang, W. K.; Choi, O. K. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1204. [c] Lodaya, J. S.; Koser, G. *J. Org. Chem.* **1988**, *53*, 210. [d] CH_3OH was used as solvent in this reaction. [e] 2 equiv of isonitrile was used in this reaction.

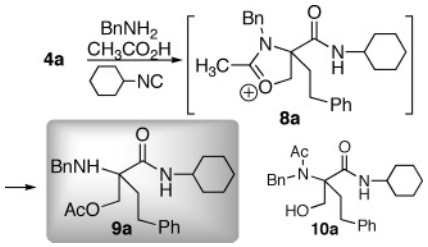
carboxylic acid ammonium salt (4 equiv) and the ketomesylate in CF_3CH_2OH for 30 min at 0 °C is sufficient to minimize the formation of Passerini products like **7**.

As the examples in Table 1 indicate, a broad range of carboxylic acids and isonitriles (including examples of both compound families derived from naturally occurring α-amino acids) underwent smooth reaction with various ketomesylates and ammonia to form the desired 2-oxazolines. Even

resonance-stabilized ketomesylates such as $PhCOCH_2OMs$ **4d** were reactive enough to form the desired oxazoline carboxamides, e.g., **6j**, in good yield.

When ammonia was replaced with a primary amine, such as benzyl or allylamine, the multicomponent reaction took a different course, affording aminoesters like **9a** (Scheme 3) as the exclusive product from ketomesylate **4a**. The

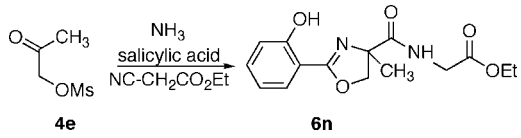
Scheme 3. MCR Route to Aminoesters from Ketomesylates **4**



structure of **9a**, which was also confirmed by single-crystal X-ray diffraction analysis, most likely arose via hydrolysis of an intermediate oxazolinium ion like **8a**. Interestingly, none of the isomeric amido alcohol **10a** was detected.

The new oxazoline synthesis could also be applied (Scheme 4) to a one-pot assembly of the 2-hydroxyphenyl-4-methyloxazoline-4-carboxamide substructure found in natural products like **1**−**3**. Initial attempts using salicylic acid as the carboxylic acid component failed in trifluoroethanol because of the insolubility of ammonium salicylate. However, the problem was overcome by switching to methanol as solvent. Gratifyingly, the desired oxazoline **6n** was produced in 63% yield. Furthermore, no phenol protecting group was required, in contrast to earlier total synthesis efforts in the mycobactin series.[8]

Scheme 4. Assembly of 2-Oxazoline Substructures in **1**−**3**



4e **6n**

In summary, we have developed an efficient four-component reaction that affords 2-substituted oxazoline-4-carboxamides in a one-pot process from readily available starting materials. With their widespread occurrence in bioactive natural products, such functionalized oxazolines may be considered privileged structures, i.e., molecular frameworks exhibiting medicinally useful binding properties. The multicomponent synthesis reported here rapidly assembles promising lead compounds containing this heterocyclic system for use in drug discovery endeavors.

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Supporting Information Available: Representative experimental procedures for the synthesis of 2-oxazolines described in Table 1, as well as supporting spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070694H

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