Organic LETTERS

Letter

pubs.acs.org/OrgLett

Facile Synthesis of Spirocyclic Lactams from β-Keto Carboxylic Acids

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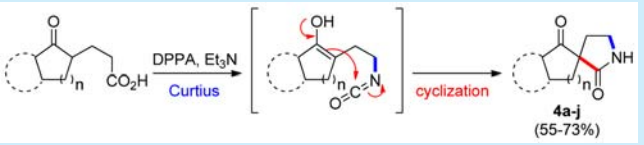
Supporting Information

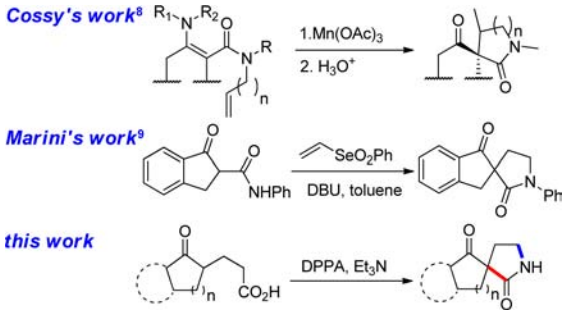
ABSTRACT: A facile synthesis of spirocyclic lactams starting from β-keto carboxylic acids via a one-pot cascade reaction involving a Curtius rearrangement and an intramolecular nucleophilic addition of the enol carbon to the isocyanate intermediate is reported. The same conditions have also been used for the generation of fused cyclic lactams with similar good yields. The synthetic value of this method has been demonstrated by efficient synthesis of tetracyclic spirolactam **8** and pentacyclic spirolactam **9**.



Spirocyclic β-keto lactam moieties are widely present in natural and pharmaceutical compounds with a broad spectrum of biological activities. Spirolactam fusarisentin A, isolated from fungus *Fusarium* sp., FN080326, is a potent inhibitor for acinar morphogenesis, migration, and invasion of cancer cells.[1] Exiguaquinol, a natural product isolated from Australian sponge *Neopetrosia exigua*, is a novel antimicrobial agent that functions by potently inhibiting the *Helicobacter pylori* glutamate racemase MurI.[2] Phomopsichalasin, the first cytochalasin-type compound isolated from an endophytic *Phomopsis* sp., is known for its antimicrobial and antifungal activities.[3] Synthetic spirolactams have demonstrated promising antagonistic activities for neuropeptide calcitonin gene-related peptide (CGRP) receptors as potential treatment for cerebrovascular disorders.[4] In addition, the 1,2,3,4-tetrahydro-β-carboline (THBC)-based spirolactams have been used mimetically as somatostatin for somatostatin receptors as potential treatment of endocrine tumors and acromegaly.[5]

Because of its unique structural features and great potential as a multifunctional scaffold in drug discovery,[6] the synthesis of spirocyclic β-keto lactams has attracted long-standing interest.[7] Several synthetic methods have been reported. For example, Cossy and co-workers reported the synthesis of spirocyclic lactams by a $Mn(OAc)_3$-catalyzed radical cyclization of unsaturated β-keto carboxamides (Scheme 1).[8] Marini and co-workers synthesized spirolactams via a domino Michael addition/cyclization process using vinyl selenone as a Michael acceptor.[9] In addition spirolactams have been prepared using ruthenium-catalyzed ring-closing metathesis[10] and palladium-catalyzed carboxycyclization.[10b,11] While these methods found applications in synthesizing spirocyclic keto-lactams, they uniformly suffered from major limitations including the lack of substrate availability, employment of environmental-unfriendly metal catalysts, harsh reaction conditions, and multistep synthesis.

Scheme 1. Routes to Spirocyclic β-Keto-lactams



The Curtius rearrangement is a commonly used reaction for the transformation of a carboxylic azide into an isocyanate,[12] which can be subsequently attacked by various nucleophiles to give different products such as carbamate,[13] ureas,[14] and thiourethanes.[15] Examples are also known where the isocyanate is attacked by a nucleophilic carbon to form a new amide bond.[16] Of these methods, an activated carbon, through either carbon metal salts[16,17] or reactive methylene, is employed.[18] The utility of the α-carbon of a carbonyl to attack the isocyanate is rarely explored.[19]

In the course of our research program on small molecule therapeutics for diffuse large B-cell lymphoma (DLBCL) and triple negative breast cancer (TNBC), we are interested in a practical synthetic method to multisubstituted spirocyclic

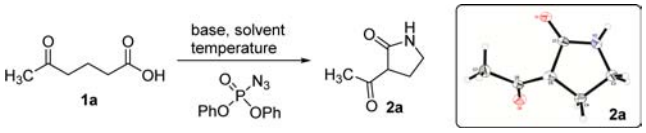
Received: May 7, 2015
Published: June 4, 2015

DOI: 10.1021/acs.orglett.5b01350
Org. Lett. 2015, 17, 3070−3073

lactams. Herein, we report a one-step synthesis of spirocyclic β-keto-lactams using δ-keto acids. To the best of our knowledge, this is the first example using the α-carbon of a carbonyl to attack the isocyanate of a Curtius rearrangement product. The current method broadens the potential application of Curtius rearrangement and complements the current synthetic methods for the preparation of spirocyclic lactams.

We first sought to identify optimal conditions for the generation of 3-acetylpyrrolidin-2-one (**2a**) from 5-oxohexanoic acid (**1a**, Table 1). After a brief survey of solvents, we found

Table 1. Conditions for the Formation of β-Keto-lactam 2a from 5-Oxohexanoic Acid 1a[a]



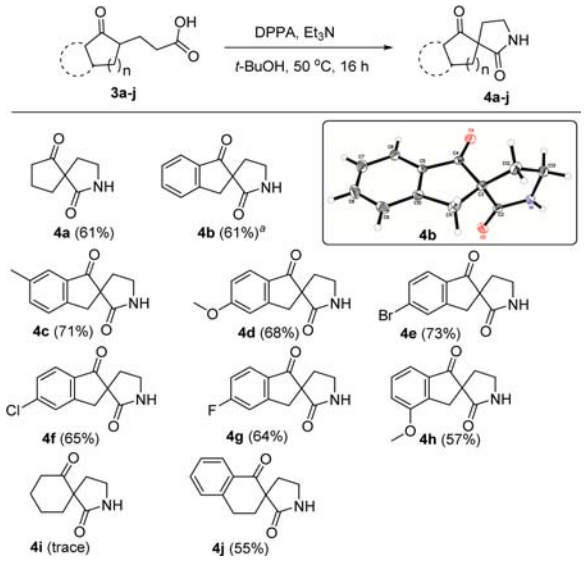
entry	solvent	base	temp (°C)	yield[b] (%)
1	DCM	Et_3N	25	<5
2	THF	Et_3N	50	<5
3	DMF	Et_3N	50	<5
4	*t*-BuOH	Et_3N	50	65
5	1,4-dioxane	Et_3N	50	10
6	toluene	Et_3N	50	31
7	*t*-BuOH	Et_3N	80	37
8	toluene	Et_3N	80	13
9	*t*-BuOH	DMAP	50	<5
10	*t*-BuOH	Cs_2CO_3	50	<5
11	*t*-BuOH	K_2CO_3	50	<5

[a]A mixture of **1a** (1.0 mmol), DPPA (1.0 mmol) and base (1.0 mmol) in 5.0 mL of solvent was stirred for 16 h. [b]Isolated yields.

that the most promising yields of compound **2a** were obtained when using *t*-BuOH as the solvent in the presence of Et_3N at 50 °C for 16 h (entry 4), whereas no obvious formation of **2a** was detected in solvents such as DCM, THF, and DMF (entries 1−3). The chemical structure of compound **2a** was confirmed by its X-ray single crystal structure (Table 1). Decreased yields were observed when the reaction was carried out in either toluene or 1,4-dioxane (entries 5 and 6). Reactions that were performed at 80 °C resulted in significantly decreased yields, indicating that higher temperature was detrimental (entries 7 and 8). Other bases were also tested, and no obvious product was formed when using bases such as carbonate and DMAP (entries 9−11).

With the optimal reaction conditions in hand, we next examined the generality of this reaction (Scheme 2). When using 3-(2-oxocyclopentyl)propanoic acid (**3a**) as the starting material, the cyclization reaction went smoothly to afford spirolactam 2-azaspiro[4.4]nonane-1,6-dione (**4a**) in good yields. Similar yields of spirolactam **4b** were obtained when 3-(1-oxo-2,3-dihydro-1*H*-inden-2-yl)propanoic acid (**3b**) was used as the starting material. Gram-scale quantities of **4b** were prepared using this method with no obvious loss of the yields. The chemical structure of compound **4b** was confirmed by X-ray crystallography (Scheme 2). Substitution of the phenyl ring was studied using 3-(1-indanone-2yl) propanoic acids **3c−h** as the substrates. Our results indicated that both electron-donating and -withdrawing substituents on the phenyl ring were tolerated and the desired products **4c−h** were isolated in good yields. X-ray crystal structures of spirolactam **4c** and **4f**

Scheme 2. Scope of Acids



[a]A reaction started with 10 mmol of **3b** gave 60% yields.

showed a similar configuration to that of compound **4b** (Supporting Information). The products containing halogen substituents can be used to construct more complex structures through cross-coupling reactions. When cyclohexanone-based starting material 3-(2-oxocyclohexyl)propanoic acid (**3i**) and 3-(1-tetralone-2yl)propanoic acid (**3j**) were used, only a trace amount of compound **4i** and modest yields of spirocyclic keto-lactam **4j** were obtained.

To explain the different yields obtained for spirolactams **4a−b** vs **4i−j**, the geometric preferences of the isocyanate intermediates **4a′**, **4b′**, **4i′**, and **4j′** were studied using molecular dynamics (MD) simulations. The isocyanates were described by the CHARMM General Force Field (CGenFF).[20] The gas-phase MD runs for the four compounds were performed using the CHARMM program.[21]

The probability distributions of the distance of C_1-C_2 for the four isocyanates from the MD simulations are shown in Figure 1. As compared to isocyanate **4i**, isocyanate **4a** showed enhanced sampling at shorter C_1-C_2 distances, indicated by the higher peak around 3.5 Å and lower peak around 4.5 Å. This may allow for a higher production rate during the reaction when the two carbons covalently bond together for the five-membered ring moieties. With an additional phenyl ring, the distance probability distributions are changed moderately.

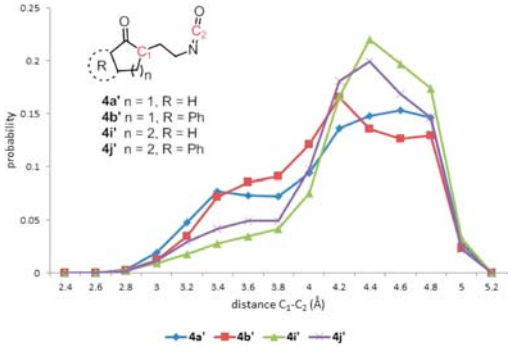


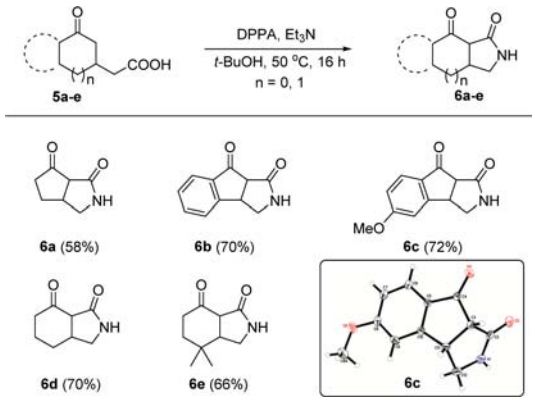
Figure 1. Probability distributions of the C_1-C_2 distance for isocyanates **4a′**, **4b′**, **4i′**, and **4j′** for MD simulations.

DOI: 10.1021/acs.orglett.5b01350
Org. Lett. 2015, 17, 3070−3073

However, compared to isocyanate **4j**, isocyanate **4b** still showed increased sampling at shorter C_1-C_2 distances around 3.5 Å. These results suggest that additional short interactions in the five-membered ring isocyanate intermediates led to their higher yields.

To further broaden the scope of this method, we studied a series of reactions using 2-(3-oxocyclopentyl) acetic acid and 2-(3-oxocyclohexyl) acetic acid derivatives (**5a−e**) as the starting material to synthesize the fused cyclic β-keto-lactams (**6a−e**). As shown in Scheme 3, under the same optimal conditions,

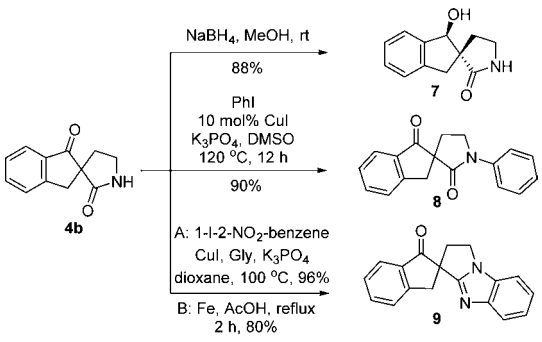
Scheme 3. Scope of Acids for Fused Cyclic β-Keto-lacatms



substrates **5a−c** reacted smoothly to give the corresponding products **6a−c** in modest to good yields. When the 3-oxocyclohexyl substrates **5d** and **5e** were used, the desired products **6d** and **6e** were obtained in 70% and 66% yields, respectively.

Since these small and rigid spirocyclic and fused keto-lactams contain multiple functional groups, they have potential as precursors in diversity-oriented synthesis (DOS) to build novel drug-like compounds. As shown in Scheme 4, diastereoselective

Scheme 4. Synthesis of Compounds 7−9



reduction of the ketone group in spirolactam **4b** using $NaBH_4$ generated alcohol **7** in good yields. The chemical structure of compound **7** was confirmed by X-ray single crystal structure (Figure 2). Cu-mediated phenylation of the amide with iodobenzene introduced another ring to offer compound **8** in high yields.[22] Furthermore, it was very impressive that Cu-mediated coupling of amide with 1-iodo-2-nitrobenzene followed by the reduction of the nitro group offered the pentacyclic spirolactam **9** in excellent yields where a new fused ring was constructed.[23]

In summary, we have disclosed a practical high-yield synthesis of spirocyclic lactams as well as fused lactams from

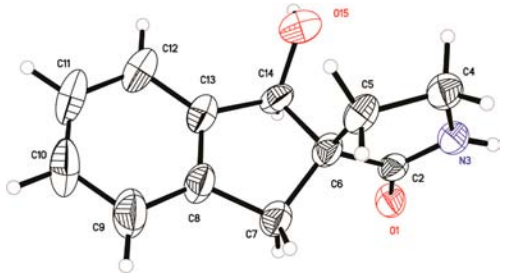


Figure 2. X-ray single crystal structure of compound **7**.

readily available β-keto carboxylic acids. The differences in yields for compounds **4a** and **4b** vs **4i** and **4j** are due to increased sampling of the shorter isocyanate carbon to ring carbon distances as evidenced by MD simulations. The value of the method has been shown in the preparation of compounds **7−9** in high yields. Further asymmetric control of the generation of the quaternary carbon center of spirolactams is being investigated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01350.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Maryland Computer-Aided Drug Design Center, the Leukemia Research Foundation, and the Samuel Waxman Cancer Research Foundation for their support of this work. The X-ray crystallographic work was supported by NIDA through Interagency Agreement No. Y1-DA1101 with the Naval Research Laboratory (NRL).

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DOI: 10.1021/acs.orglett.5b01350
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