Synthesis of γ-Lactams from Acrylamides by Single-Carbon Atom Doping Annulation

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Supporting Information Placeholder

ABSTRACT: A protocol for single-carbon atom doping annulation is reported, which enables the conversion of acrylamides into homologated γ-lactams through the cleavage of two σ-bonds and the formation of four new σ-bonds at the single carbon center. The key strategy is the use of N-heterocyclic carbenes as an atomic carbon equivalent, which act as carbon atom donors through the loss of a 1,2-diimine moiety. Experimental and computational studies reveal that the reaction proceeds through a spirocyclic intermediate, followed by the disassembly of the N-heterocyclic carbene skeleton via a proton transfer.

An atomic carbon, which represents an electronically neutral carbon-based species that contain the smallest number of electrons, would be an attractive reactive intermediate because it could be used in chemical transformations that permit four covalent bonds to be formed at one carbon center in a single step.[1] The simplest transformation induced by an atomic carbon is a single-carbon atom doping (SCAD) reaction, in which one carbon atom is inserted into the starting molecule.[2] Among the SCAD reactions, SCAD annulation would serve as a powerful tool for the synthesis of cyclic compounds via the insertion of an atomic carbon into two σ-bonds in the starting molecule to form a new ring (Figure 1a). SCAD annulation is, in fact, reported to proceed by reactions using an atomic carbon that can be generated by several physical methods.[3] For example, in the reaction of an arc-generated atomic carbon with *tert*-butylbenzene ($C_{10}H_{14}$), the carbon atom is inserted into two σ-bonds to produce a ring motif, resulting in the formation of an indane derivative ($C_{11}H_{14}$) (Figure 1b).[3b] However, the need for a complex apparatus as well as the extremely short lifetime of an atomic carbon limits the utility of this reaction in the context of synthetic organic chemistry. Herein we report on the use of N-heterocyclic carbenes (NHCs) as an atomic carbon equivalent, which functions as a single carbon atom donor to convert acrylamides into γ-lactams by SCAD annulation (Figure 1c).

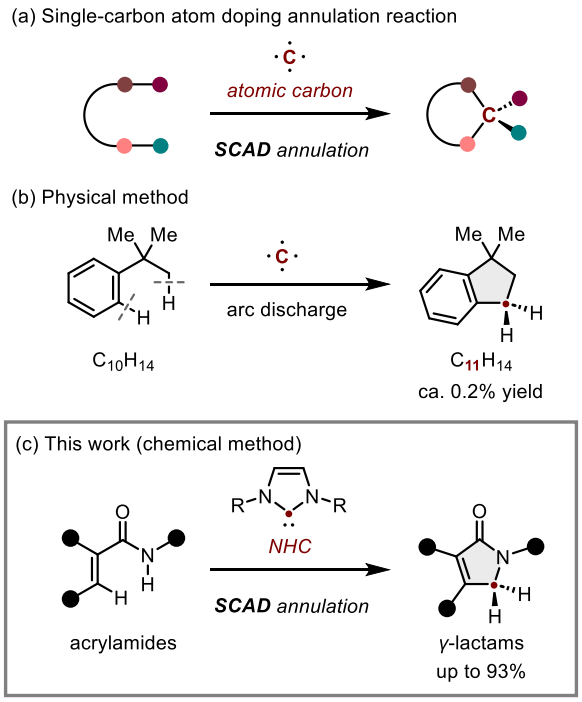


Figure 1. SCAD annulation reactions.

Quite recently, we reported on the first chemical SCAD reaction for producing N-aryl acrylamides using NHC as a carbon atom source (Figure 2a).[2] The reaction is initiated by the 1,4-addition of NHC across an acrylamide, which leads to the formation of an ylide intermediate **I**.[4,5] The ylide **I** is sufficiently nucleophilic that it can attack the carbon ipso to the nitrogen on the aromatic ring, resulting in an S_NAr reaction. The dissociated amide anion subsequently adds to the imidazolium moiety to generate spiro intermediate **II**.[2] We envisioned that this postulated spiro intermediate could be formed from simpler N-H acrylamides if the proton on the nitrogen could abstract the ylide intermediate.[6] The development of this variant would significantly expand the scope of SCAD annulation reactions. Based on this hypothesis, the reaction of the acrylamide **1a** with **N1**•HBF_4 as a carbon atom source was initially examined (Figure 2b). However, only trace amounts of the desired annulation product **2a** was produced and the tale-to-tale dimerization product **3a** was produced as the major product.[7] In contrast, the tiglic amide **1b** afforded the expected SCAD annulation product **2b** in 93% yield (Figure 2c). These results indicate that the substituent at the

β-position effectively suppresses the undesired tale-to-tale dimerization pathway, thereby promoting SCAD annulation.

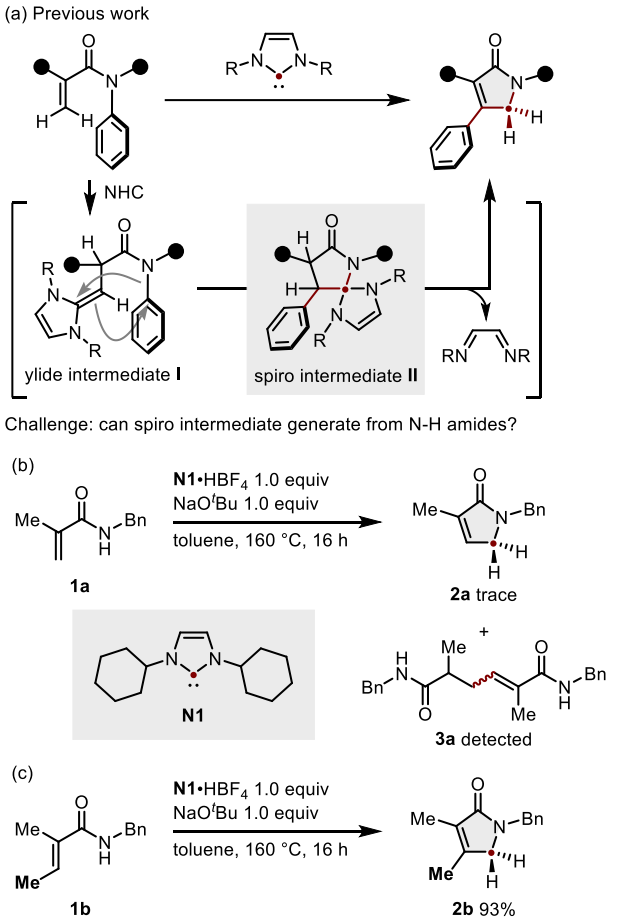
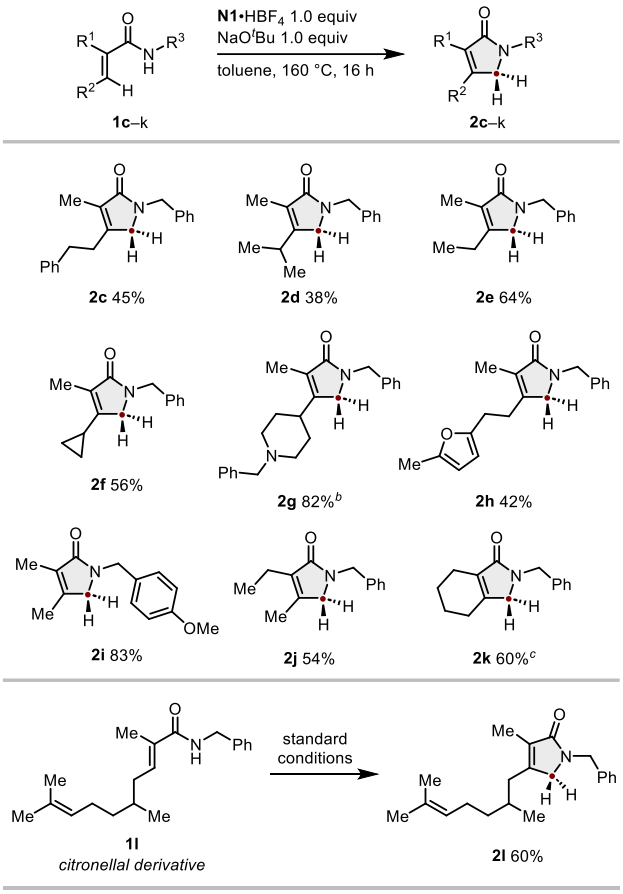


Figure 2. Working hypothesis.

The SCAD annulation reaction can be used for a range of acrylamide derivatives (Scheme 1). Acrylamides bearing phenethyl (**1c**), isopropyl (**1d**), ethyl (**1e**), and cyclopropyl (**1f**) groups readily participated in this reaction to form the corresponding γ-lactam derivatives. Heterocycles such as the piperidine (**1g**) and the furan (**1h**) are also well-tolerated under these SCAD annulation conditions. This reaction proceeded successfully when a *p*-methoxybenzyl group (**1i**) was used as a protecting group for the nitrogen atom. Regarding the substituents at the α-position, an ethyl group was compatible with this reaction to produce γ-lactam **2j**, which is a key building block for the synthesis of the natural pigment phycobilin[8] and the antidiabetic drug glimepiride.[9] A cyclic amide also participated in this reaction, resulting in the production of the corresponding γ-lactam **2k** in 60% yield. Crotonic amides and cinnamamides failed to form the corresponding lactams (see SI). A derivative of citronellal (i.e., **1l**) could also be converted into the corresponding γ-lactam **2l** in 60% yield, with the other alkene moiety remaining intact. Compared with previously reported synthetic methods for producing α,β-unsaturated γ-lactams,[10] SCAD annulation provides a highly straightforward strategy using readily available acrylamides and NHCs, thereby allowing for the facile access to elaborate γ-lactams, as demonstrated in Scheme 1.[11]

Scheme 1. Scope of the SCAD Annulation Reaction of Acrylamides[a]



[a]Reaction conditions: acrylamide (0.20 mmol), **N1**•HBF_4 (0.20 mmol), NaO^{t}Bu (0.06 mmol), and toluene (1.0 mL) in a sealed tube at 160 ºC for 16 h. Yields of isolated products are shown. [b]The reaction was run at 120 ºC. [c]The reaction was run using **N2**•HBF_4.

Several experiments were performed in an attempt to gain insights into the reaction mechanism (Figure 3). When **N2** was used as a carbon atom source in the reaction of amide **1k**, the 1,2-diimine **4** was isolated in addition to the γ-lactam **2k**, which suggests that the C2 carbon of **N2** served as an atomic carbon equivalent (Figure 3a). When the reaction of **1k** with **N2** was carried out at lower temperature of 120 °C, we successfully isolated the diamide **5k** in 53% yield, which was presumably produced by hydrolysis of the ortho amide moiety in the postulated spiro intermediate. (Figure 3b).[12] The structure of **5k** was unambiguously determined by converting it into the hydrolysis product, the ketone **6k**, the structure of one of the diastereomers was successfully determined by X-ray crystallography.[13] These results support the intermediacy of a spiro intermediate in this SCAD annulation reaction.[14] A deuterium labeling experiment was also performed to investigate the origin of the methylene hydrogen atoms (Figure 3c). When amide **1b**-d_5 in which the vinylic hydrogen, hydrogen on the nitrogen, and a β-methyl group were labeled with deuterium atoms, was reacted with **N1** under the standard reaction conditions, the γ-lactam **2b**-***d*** was obtained. As expected, the deuterium atoms were incorporated into the γ-position of the lactam ring, although the deuterium content was only 35%, due to rapid H/D exchange between other relatively acidic C–H bonds in **2b** (the *N*-benzyl position: 32% D, the β-methyl group: 39% D).[2]

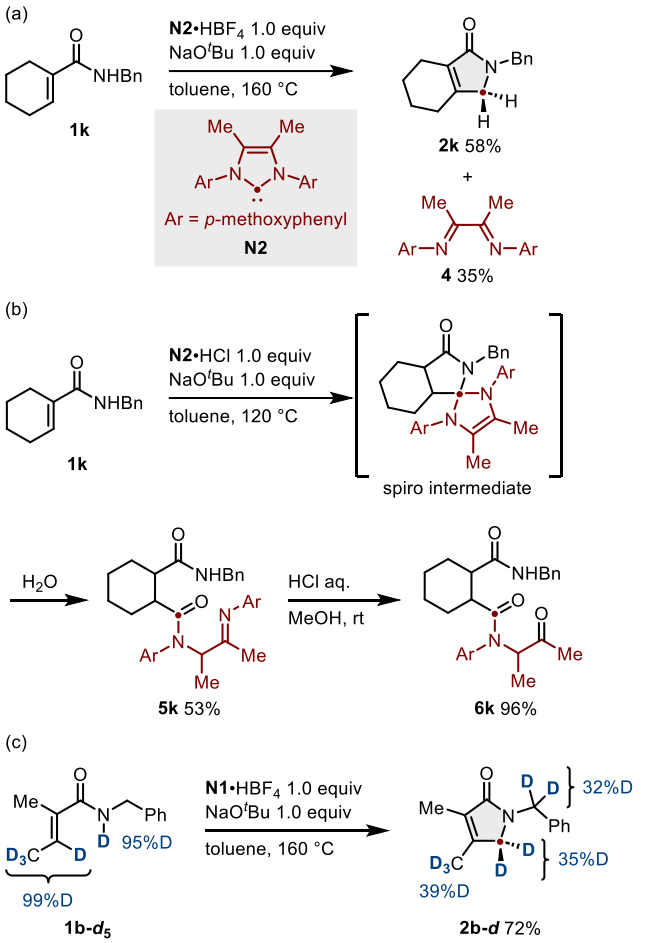


Figure 3. Mechanistic studies.

To gain additional insights into the SCAD process, DFT calculations were performed using the amide **1m** as the model substrate (Figure 4). The results indicate that **N1** undergoes a 1,4-addition to **1m** via **TS1** with an activation free energy of 26.3 kcal/mol to form the enolate **IM1**. A subsequent proton shift affords the amide anion **IM2**, which undergoes an intramolecular 1,2-addition of the amide anion to the imidazolium moiety, leading to the formation of the spiro intermediate **IM3**. The formation of **IM3** is exoergonic by 5.2 kcal/mol compared with the starting materials. One of the C–N bonds derived from NHC in **IM3** is subsequently cleaved to form the iminium intermediate **IM4** with an activation free energy of 29.9 kcal/mol. **IM4** then isomerizes to form the enamine **IM5**, followed by a 1,3-proton shift to afford the more stable intermediate **IM6**. It should be noted that a similar C–N bond cleavage of an ortho amide was reported in a previous study.[15] The second C–N bond cleavage is facilitated by the deprotonation of **IM6** to generate the anion **IM7**, which dissociates into the 1,2-diimine **7** to form the cyclic dienolate **IM8** with an activation barrier of 28.1 kcal/mol. Finally, the protonation of **IM8** forms the γ-lactam **2m** (proton pathway). An alternative pathway involving the formation of a pyrrolium cation **IM9**, followed by hydride reduction was found to be energetically much less favored (hydride pathway).[16]

In conclusion, we report on the development of a NHC-mediated SCAD annulation reaction, which allows for the conversion acrylamides into γ-lactams through the formation of four single bonds to one carbon center in one operation. This study demonstrates the potential utility of a SCAD process in synthetic organic reactions. Further studies directed to the development of new SCAD reactions are currently underway in our laboratory.

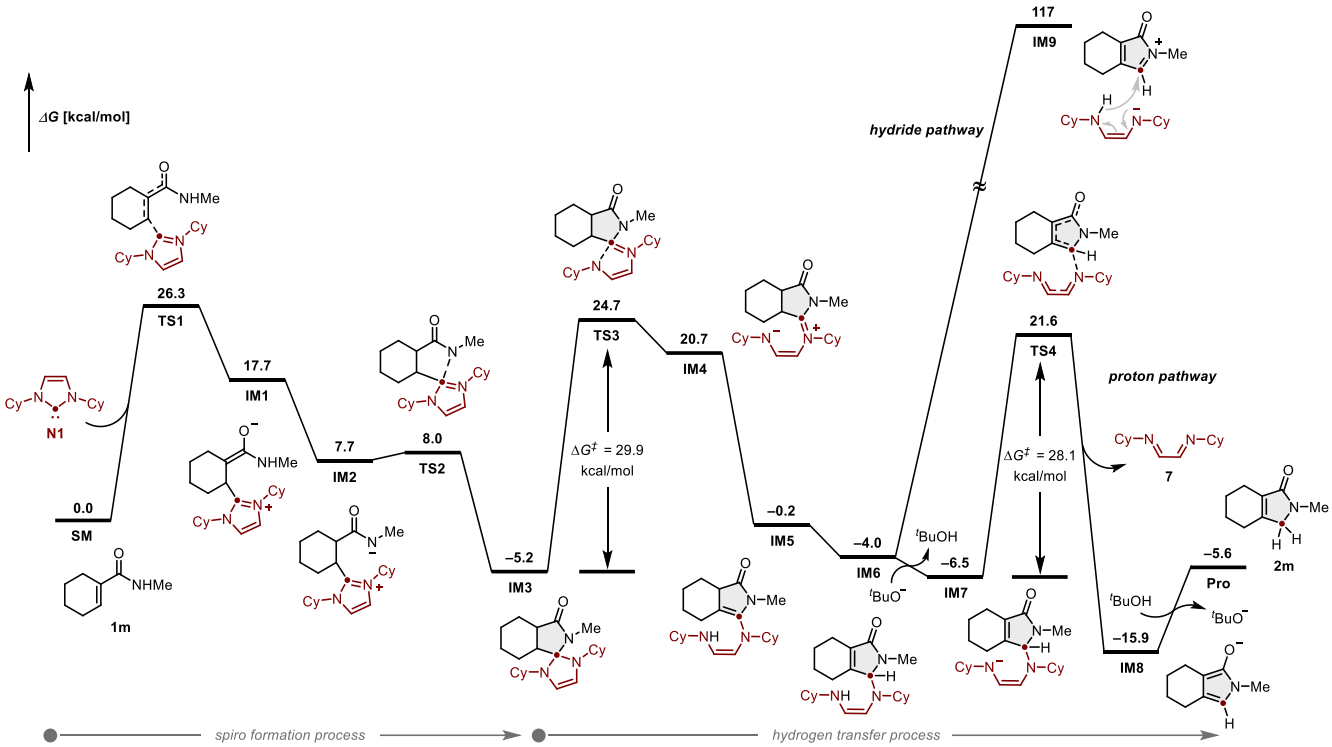


Figure 4. Mechanistic studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed experimental procedures, characterization of new compounds and computational details (PDF)
Compound **6k** crystal structure (CIF)

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Notes

The authors declare no competing financial interests.

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(13) Crystal data for **6k**, monoclinic, space group $P\ 2_1/n$, a = 13.4256(3) Å, b = 11.7382(2) Å, c = 16.2461(4) Å, α = 90 º, β = 111.228(2) º, γ = 90 º, V = 2386.54(9) Å^3, T = 123 K, Z = 4, R_1 (wR_2) = 0.0676 (0.1907) for 408 parameters and 4969 unique reflections. GOF = 1.056. CCDC 2272222.

(14) The existence of the spiro intermediate is also supported by a direct high-resolution mass spectrometry (HRMS) analysis of the crude reaction mixture. A signal with *m/z* of 524.2935 was observed, which matches the *m/z* of the spiro intermediate (calcd for [M+H$^+$]: 524.2908).

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