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Intramolecular Schmidt Reaction of Vinyl Azides with Cyclic Ketones

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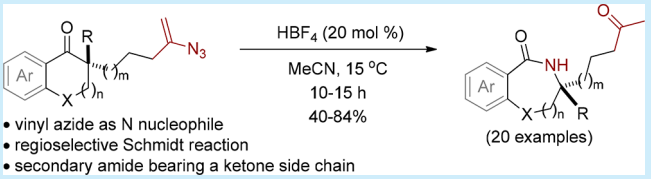
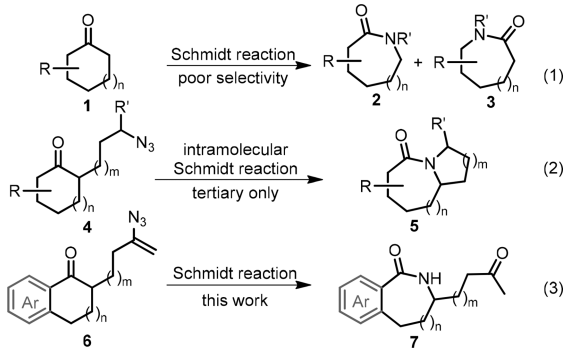
Supporting Information

ABSTRACT: Cyclic ketones tethered with a vinyl azide group undergo a Schmidt-hydrolysis sequence to give secondary lactams bearing a ketone side chain. Secondary lactams are obtained in a regioselective manner that is not possible in a conventional Schimdt reaction. In addition to the well-documented C-2 nucleophilicity, the N nucleophilicity of vinyl azide disclosed in this work opens a new direction for reaction invention involving vinyl azides.



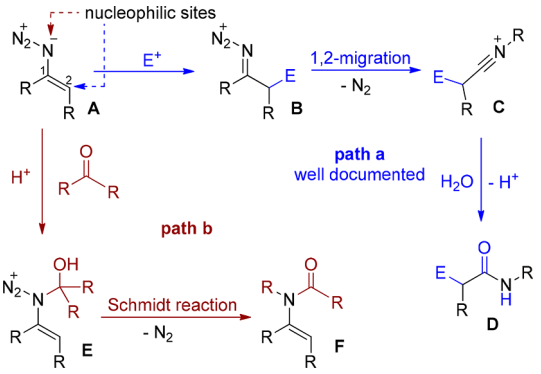
Schmidt reactions[1] of cyclic ketones are an extremely practical and efficient method for the preparation of both synthetically and biologically important lactams, especially for δ- and ε-lactams.[1d] However, the problematic regioselectivity issue for unsymmetrical ketones deteriorates their synthetic potential (Scheme 1, eq 1).[2] An intramolecular Schmidt reaction has been developed to solve this issue,[3] but this strategy is not viable for the synthesis of secondary lactams because only bicyclic tertiary lactams would be obtained through this method (Scheme 1, eq 2). Herein, we report an intramolecular Schmidt reaction that can complementarily deliver secondary lactams with a ketone side chain through the reaction of vinyl azides with cyclic ketones (Scheme 1, eq 3).

Scheme 1. Comparison of Conventional Schmidt Reactions with Schmidt Reaction of Vinyl Azide



In the course of our studies on azirine, we became interested in the chemistry of vinyl azide.[4] Attributed to its diverse reactivities, this unique functional group has been used as versatile synthons for various transformations.[5] It can be used as azirine precursor,[6] nitrene progenitor,[7] radical receptor,[8] (formal) 1,3-dipole,[9] 1,3-dipolephile[10] and latent nitrilium ions,[11] etc. Electrophilic attack on or protonation of vinyl azide **A** at C2 would give diazonium cation **B**, which could undergo 1,2-migration to generate nitrilium ions **C**; subsequent hydrolysis would afford secondary amide **D** (Scheme 2, path a). This chemistry had been discovered by the Moore[12] and Hassner groups,[13] and advanced by the groups of Chiba,[11c,d] and Jiao.[14] We were curious whether the vinyl azide, just like alkyl azide[15] in a Schimdt reaction, could serve as a *N*-nucleophile that could attack an activated carbonyl group by the internal nitrogen atom to form diazonium cation **E** and then *N*-vinyl amide **F**, as operated in a conventional Schmidt reaction (Scheme 2, path b). To the best of our knowledge, this reactivity is not well documented for vinyl azide.

Scheme 2. Vinyl Azide Acting as *C*-Nucleophile and *N*-Nucleophile



At the outset, phenyl vinyl azide was subject to reaction with benzocyclohexan-1-one in the presence of 20 mol % fluoroboric acid (48% HBF_4 aqueous solution) in acetonitrile at rt; *N*-phenylacetamide was obtained (71%) with full recovery of the cyclic ketone (Scheme 3). These outcomes indicated that no intermolecular Schmidt reaction occurred; instead, protonation/1,2-migration sequence took place (Scheme 2, path a).

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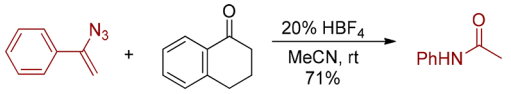
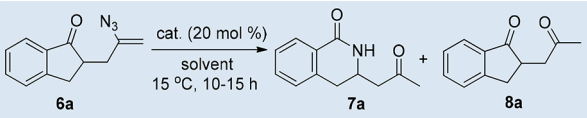
Scheme 3. Acid-Promoted Hydrolysis of Phenyl Vinyl Azide in the Presence of Benzocyclohexan-1-one



It was envisioned that the kinetically favored intramolecular process might help to facilitate the Schmidt pathway to outcompete path a. Thus, vinyl azide **6a** with a dihydroindenone group in proximity was chosen for this purpose, and conditions for a conventional Schmidt reaction were evaluated with it (Table 1). To our delight, with 20 mol % Lewis acid

Table 1. Condition Optimization for Intramoleclar Schmidt Reaction of Vinyl Azide[a]



6a 7a 8a

entry	catalyst (20 mol %)	solvent	7a, yield[b] (%)	note
1	$BF_3{\cdot}Et_2O$	MeCN	65	**6a**, 30%
2	$TiCl_4$	MeCN	52	complex
3	CF_3CO_2H	MeCN	27	**6a**, 25%
4	TfOH	MeCN	34	31% **8a**[c]
5	MsOH	MeCN	48	**8a**, 37%
6	H_2NSO_3H	MeCN	NR	**6a**, 95%
7	HBF_4	MeCN	84	**8a**, 12%
8	HBF_4	DCM	61	**8a**, 33%
9	HBF_4	DCE	56	**8a**, 34%
10	HBF_4	PhMe	31	**8a**, 56%
11	HBF_4	MTBE	21	**8a**, 58%
12	HBF_4	CF_3CH_2OH	68	-

[a]**6a** (50 mg, 1.0 equiv), solvent (3 mL), catalyst (20 mol %) at 15 °C for 10−15 h. [b]Isolated yield. [c]21% revovery of **6a**.

$BF_3{\cdot}Et_2O$, the desired reaction did occur at 15 °C to give a Schmidt-type product lactam **7a** in 65% yield, but with 30% starting material kept intact (entry 1). $TiCl_4$ shows higher catalytic ability, albeit resulted in a more complex reaction mixture (entry 2). Bronsted acid CF_3CO_2H was less efficient than $TiCl_4$ as only partial conversion of **6a** was observed after 15 h in MeCN (entry 3). Treatment with 20 mol % TfOH led to a mixture of 21% **6a**, 34% **7a**, and a diketone **8a** in 31% yield, a product derived from vinyl azide hydrolysis (entry 4). Interestingly, full conversion was achieved with MsOH as catalyst to give 48% **7a** and 37% **8a** (entry 5), but sulfamic acid was totally ineffective (entry 6). Complete reaction was achieved with 20 mol % HBF_4 (48% aqueous solution) to yield **7a** in 84% isolated yield with 12% **8a** (entry 7). Chlorinated solvents DCE and DCM afforded deteriorated selectivity (entries 8 and 9). When performed in nonpolar solvents toluene and methyl *tert*-butyl ether (MTBE), the reaction gave diketone **8a** favorably (entries 10 and 11), while in CF_3CH_2OH, a complex mixture was obtained from which **7a** was isolated in 68% yield (entry 12).

The use of HBF_4 (20 mol %) in MeCN (Table 1, entry 7) were adopted as the standard conditions for further studies and, in order to explore the substrate scope, a diversity of vinyl azides **6b−t** were made and submitted to these conditions (Table 2). Vinyl azide **6b** with an additional α-carboxylate group reacted smoothly to give cyclic amide **7b** with a normally difficult amide-substituted quaternary carbon center. Vinyl azides **6c−e**, derived from benzofused cyclohexanones, were also feasible for this reaction, albeit giving corresponding cycloheptamides **7c−e** in lower yields. One carbon elongation of the tether between the groups of cyclic ketone and vinyl azide results in **6f**, which was converted to lactam **7f** in 56% yield under the standard conditions. Installation of a carboxylate group at the α-position improves the reaction dramatically, as demonstrated by 81% **7g** from **6g**. Three methylene linked vinyl azide **6h** was also converted to the Schmidt lactam **7h** in 64% yield with 32% **8h**. Similarly, a high yield of 85% of **7i** was also obtained with substrate **6i**. Fluorination on the aryl ring does not affect the reaction significantly, as lactams **7j** (79%) and **7k** (74%) were obtained in good yields. Interestingly, though benzo-fused cyclohexanone **6l** reacted equally as well as cyclopentanone analogous **6h** did (70% **7l**), **6m** could not provide better yield as **6i** did (40% **7m** vs 85% **7i**). The use of an electron-releasing methoxyl group showed a beneficial effect on the reaction, and lactam **7n** was collected in 82% yield. Incorporation of a NTs moiety in the linker led to a messy reaction, and only 36% of Schmidt product **7o** was isolated even after 20 h. Pleasingly, with propylene as the tether, nonbenzo-fused cyclic ketones **6p−t** are all excellent substrates for this HBF_4-promoted Schmidt reaction, and related lactams were produced in high yields up to 87%.

When non-benzofused cyclic compounds **9a−i** with a one-carbon linker between the carbonyl group and the vinyl azide moiety were treated with the standard conditions, only diketones **10a−i** were collected without any detection of the corresponding lactams, indicating that the vinyl azide hydrolysis outcompetes other pathways. The presence of an alkene group in **9e** may cause additional side reactions leading to a decrease in the yield of **10e**. In the case of **9j**, a tertiary amine group in the molecule necessitates 1.2 equiv of HBF_4 to achieve a complete conversion. Interestingly, a mixture of unidentified products was formed for the reaction of vinyl azide **9k**.

According to Hassner's report,[13] a brief mechanism to accommodate the formation of these two types of products is summarized in Scheme 4. Protonation of vinyl azides **6**/**9** at C2 results in intermediate **III**, subsequent hydrolysis affords diketones **8**/**10** via **IV** (Scheme 4, route B); meanwhile, attack of the proton activated carbonyl group by the azide group delivered cyclic intermediate **I**, which is transformed to lactam **II** through Schmidt rearrangement and is further hydrolyzed to open up the ring giving 7 (route A). Our studies show that vinyl azides **9a−j** bypassed route A, probably due to the unfavorable formation of intermediate **I** possessing a fused 5-membered ring (m = 0) and/or subsequent formation of strained β-lactam **II** (m = 0). Benzofusion improves the reactivity of carbonyl group toward protonation and, therefore, could render route A preferred for **6a−e**. As for **6p−t**, the formation of flexible 7-membered cyclic intermediates **I** (m = 2) would assist it in adopting a conformation with perfect orbital alignment for subsequent nitrogen extrusion-alkyl group migration event to give energetically favorable six-membered bicyclic intermediates **II** (m = 2). Collectively, these benefits

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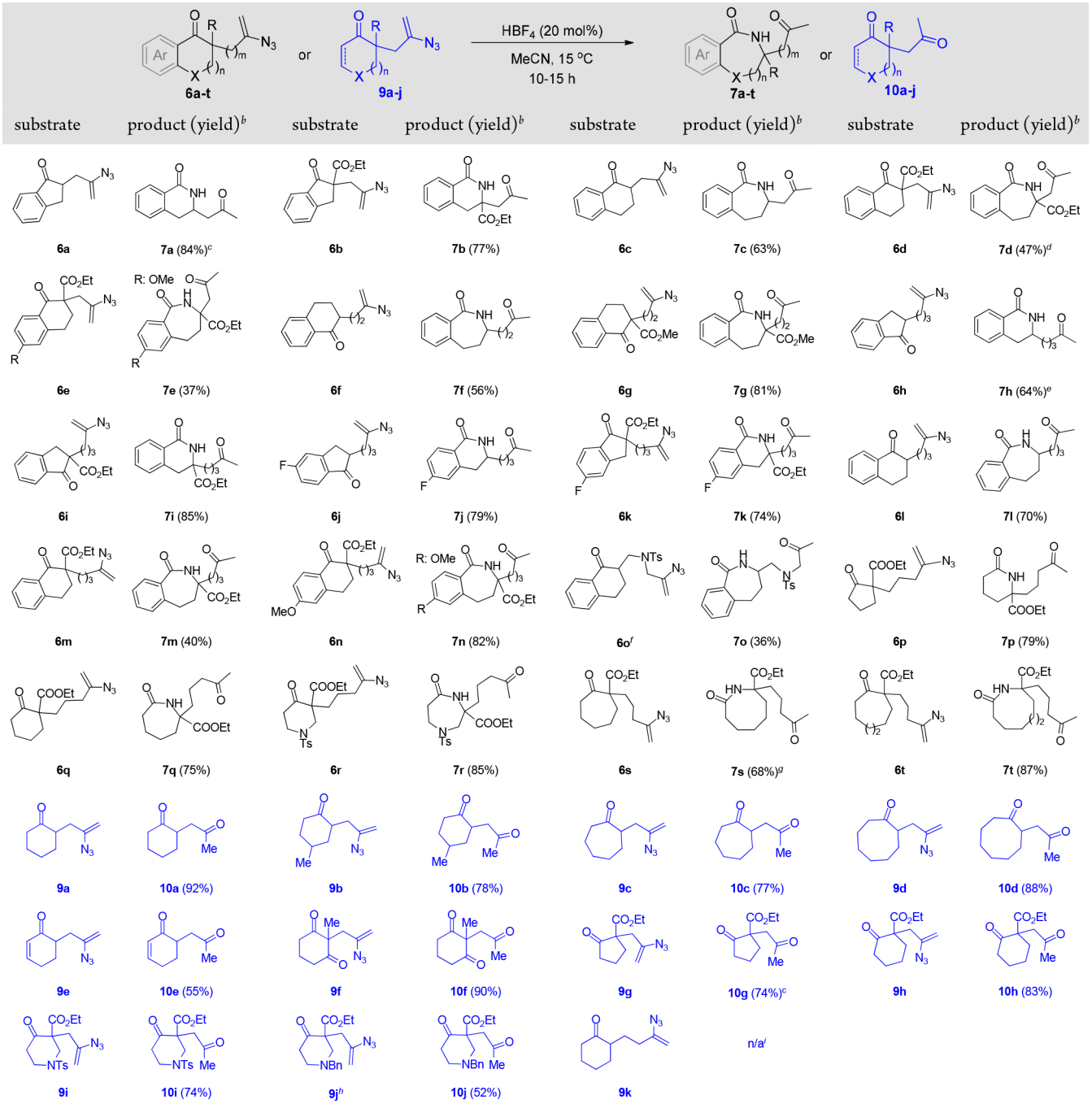
Table 2. Intramolecular Schmidt Reaction of Vinyl Azides with Cyclic Ketone and Hydrolysis of Vinyl Azides[a]



[a]**6** (50 mg, 1.0 equiv), MeCN (3 mL), HBF_4 (20 mol %) at 15 °C for 10−15 h. [b]isolated yield. [c]12% **8a** was collected. [d]Inseparable mixture, NMR yield. [e]32% **8h** was collected. [f]20 h. [g]22% **8s** was collected. [h]1.2 equiv of HBF_4 was used. [i]Mixture of unidentified products was obtained (4 times of repetition).

must make the transformations through route A be fast enough to outcompete corresponding vinyl azide hydrolysis (Scheme 4, route B). The divergent chemoselectivity shown between **6** and **9** and the exclusive formation of lactams **7** without their regioisomers **7′** rules out an alternative pathway in which HN_3 generated by route B reacts with the cyclic ketone intermolecularly. It is worth noting that, for many substrates other than **6a**, **6h**, and **6s** in Table 2, their hydrolytic products of type **8** have also been observed but were difficult to collect in pure form by silica gel column chromatography.

To gain more information for this reaction, acyclic substrate **11** was prepared and submitted to the standard conditions. Unlike its cyclic congener **6c**, the reaction of **11** produced diketone **14** in 56% yield and the intramolecular Schmidt product **12** in only 12% yield, along with 8% inseparable amide **13** (Scheme 5). This might be attributed to the reduced flexibility in cyclic ketone that favors an intramolecular process.

In summary, we have developed a novel intramolecular Schmidt-hydrolysis sequence that affords secondary lactams with a ketone side chain in exclusive regioselectivity that is impossible for conventional Schimdt reactions and, therefore,

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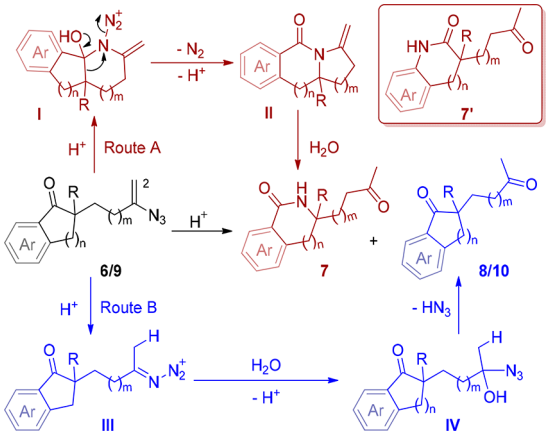
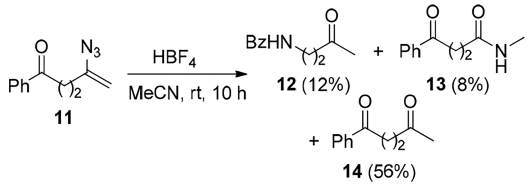
Scheme 4. Mechanistic Explanation for the Formation of 7 and 8/10



Scheme 5. Reaction of Acyclic Substrate 11



will greatly expand the application range of the Schmidt reaction. In contrast to the well-documented C nucleophilicity for vinyl azide, this group herein serves as an N-nucleophile to attack the tethered carbonyl group, initiating a Schmidt process. This new reactivity not only is very significant from a mechanistic point of view but also opens an additional direction to disclose new reactions for vinyl azides. It is also found that for certain substrates direct hydrolysis of the vinyl azide dominates the reaction to form diketones. The length of the linker plays an important role for this chemoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00395.

Experimental procedures, characterization data, and NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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