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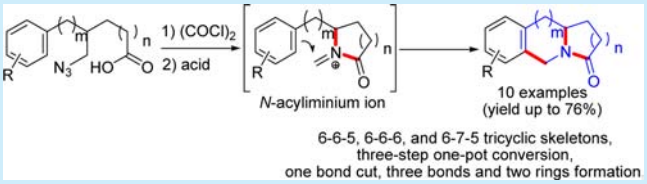
Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides: Capture of *N*-Acyliminium Ion Intermediates with Aromatic rings

Xiao-Jing Li, Jin-Bao Qiao, Jian Sun, Xue-Qiang Li, and Peiming Gu*

Key Laboratory of Energy Sources & Engineering, State Key Laboratory Cultivation Base of Natural Gas Conversion and Department of Chemistry, Ningxia University, Yinchuan 750021, China

Supporting Information

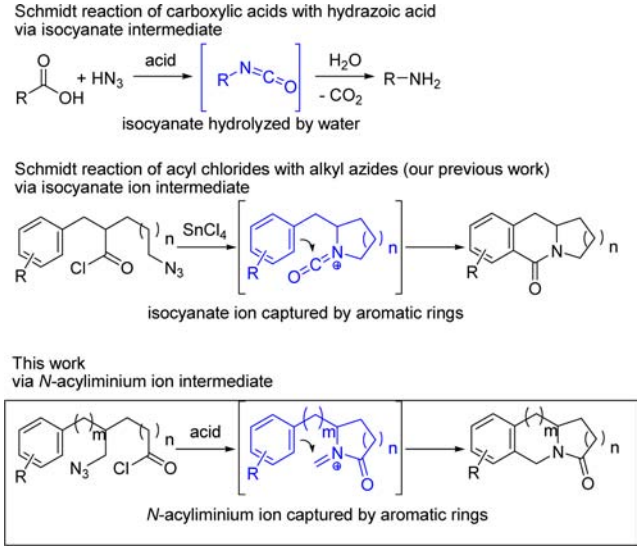
ABSTRACT: Intramolecular Schmidt reaction of acyl chlorides with alkyl azides through *N*-acyliminium ion intermediates is designed and realized. The intramolecular capture of the intermediates with aromatic rings affords several nitrogen-containing tricyclic skeletons. The important feature of the domino process is the efficiency in bond reorganization and ring formation.



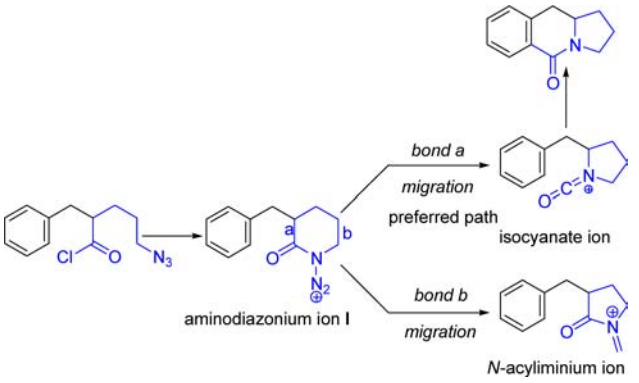
The Schmidt reaction of electrophiles with hydrazoic acid (HN_3) was extensively explored in early studies.[1] In the 1990s, the replacement of HN_3 with alkyl azides was proven very successful in the Schmidt reaction of aldehydes,[2−4] ketones[5] and carbocations.[6] Inspired by the strategy, an intramolecular Schmidt reaction of ω-azido acyl chlorides (formed from ω- azido carboxylic acids with oxalyl chloride) through isocyanate ion intermediates was reported with our effort (Scheme 1).[7] In this paper, we present a new type of intramolecular Schmidt reaction of the designed ω-azido acyl chlorides featured with *N*-acyliminium ion intermediates.

In the previous paper, 1,2-migration of the methine carbon next to the carbonyl group of the aminodiazonium ion intermediate **I** (Scheme 2) resulted in an isocyanate ion intermediate with loss of nitrogen gas, which was captured by an aromatic ring to afford the benzo fused lactam. But if the 1,2-migration of the methylene carbon on the right took place, the *N*-acyliminium ion intermediate would be produced.

Scheme 1. Schmidt Reaction of Carboxylic Acids or Acyl Chlorides



Scheme 2. Schmidt Reaction of Acyl Chloride through Isocyanate Ion Intermediate



The migration aptitude of the substituted carbon increased with the size of the substituent, which was observed in the reaction of ketones with hydroxyalkyl azides.[8] Thus, if the *N*-acyliminium ion intermediate was desired, the sensitive approach would be to increase the tendency of migration of *bond b* and limit the migration of *bond a* in the aminodiazonium ion intermediate **I**. We envisioned that if the benzyl group (Scheme 2) was transferred from the left carbon to the right carbon, then the substrate would be a new ω-azido acyl chloride (Scheme 3). Migration of the methine group would be preferred over the methylene group; as a result, formation of the *N*-acyliminium ion **III** would take place, and meanwhile, the competitive generation of isocyanate ion intermediate would be strongly limited. Another advantage of this strategy is that the

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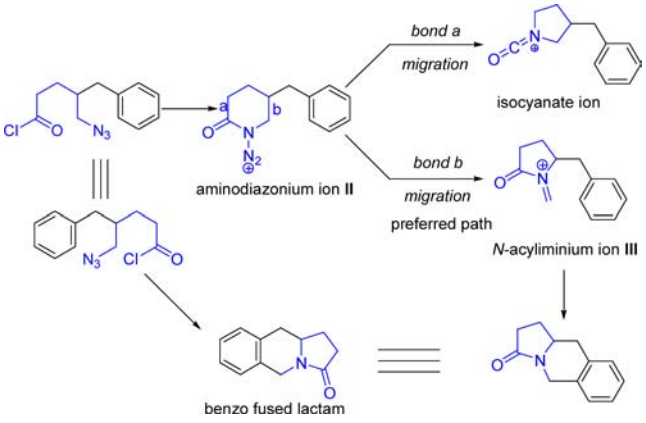
Scheme 3. Designed Schmidt Reaction of Acyl Chloride through *N*-Acyliminium Ion Intermediate



benzyl group would be in the suitable position, which would offer an aromatic ring for the subsequent intramolecular capture of the *N*-acyliminium ion.

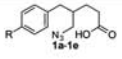
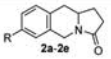
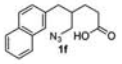
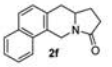
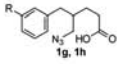
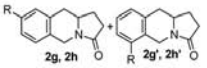
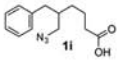
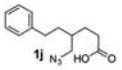
To test our proposal, the ω-azido carboxylic acid **1a** was prepared. Several acids were examined as the promoters, but no desired lactam **2a** was afforded. The poor reactivity of the Schmidt reaction of carboxylic acid with alkyl azide was demonstrated convincingly as before.[7] Treatment of the azido carboxylic acid **1a** with $(COCl)_2$ followed by the addition of $SnCl_4$ succeeded in formation of the lactam **2a**[9] in 75% yield (Table 1, entry 1). The lactam could also be delivered in 67% yield by exposure of the azido carboxylic acid **1a** with $(COCl)_2$ followed by $TiCl_4$.

To our delight, the successful conversion of carboxylic acid **1a** to lactam **2a** indicated the reaction proceeded with the following three stages: (1) the in situ generation of the ω-azido acyl chloride was achieved by treatment of carboxylic acid with oxalyl chloride; (2) the attack of the azido group upon the carbonyl group of acyl chloride initiated the rearrangement of the aminodiazonium ion intermediate, resulting in *N*-acyliminium ion **III**; and (3) the intramolecular Pictet–Spengler cylization[10] of the *N*-acyliminium ion with the aromatic ring spontaneously furnished the fused polycyclic oxobenzoindolizidine. The wonderful efficiency of the conversion was embodied in the combination of acyl chlorination, Schmidt reaction of the acyl chloride, and Pictet–Spengler cyclization. During the process, two new rings were constructed, one bond was broken, and three new bonds were formed.

We then explored the scope of azido carboxylic acids, and a series of ω-azido carboxylic acids **1b–j** were submitted to the acidic conditions. Not surprisingly, all of them were converted to the desired lactams. Introduction of methoxyl group on the aromatic ring slightly decreased the yield in the presence of $SnCl_4$ (Table 1, entry 3). But if TfOH was applied, the yield of lactam **2b** was increased to 68% (Table 1, entry 4). The methyl group had similar effects on the conversion with that of methoxyl group (Table 1, entries 5 and 6). The electron-withdrawing groups on the aromatic ring exhibited good flexibility for this conversion (Table 1, entries 7–9). Only one lactam **2f** was obtained from the reaction of the 2-naphthyl analogue azide **1f**, which indicated the cyclization took place at the more reactive α-position of naphthyl ring (Table 1, entries 10 and 11). When the meta-substituted aromatic rings were used, mixtures of regioisomers were obtained from the Pictet–Spengler cyclization. $SnCl_4$, $TiCl_4$, and TfOH were examined for the azides **1g** and **1h**. The first two promoters ensured the efficiency of the conversion of azides **1g** and **1h** but with poor regioselectivities, while TfOH gave the corresponding lactams in slightly better regioselectivities with poor yields (Table 1, entries 12–17). The $SnCl_4$-promoted reaction of the azido acid **1i** afforded benzoquinolizidine **2i** in 34% yield, whereas the $TiCl_4$ conditions gave lactam in 57% yield (Table 1, entries 18 and 19).

The benzopyrroloazepine **2j** was obtained in 71% yield when the ω-azido carboxylic acid **1j** was allowed to react with $SnCl_4$

Table 1. Intramolecular Reaction of Alkyl Azides with Acyl Chlorides[a]

entry	azides **1**	**2**, yield		conditions[c]
				
1	**1a**, R = H	**2a** (75)		$SnCl_4$, 4 h
2	**1a**, R = H	**2a** (67)		$TiCl_4$, 15 h
3	**1b**, R = OMe	**2b** (53)		$SnCl_4$, 4 h
4	**1b**, R = OMe	**2b** (68)		TfOH, 4 h
5	**1c**, R = Me	**2c** (65)		$SnCl_4$, 20 h
6	**1c**, R = Me	2c (71)		TfOH, 20 h
7	**1d**, R = Cl	**2d** (71)		$SnCl_4$, 4 h
8	**1e**, R = Br	**2e** (68)		$SnCl_4$, 20 h
9	**1e**, R = Br	**2e** (69)		$TiCl_4$, 20 h
				
10	**1f**	**2f** (54)		$SnCl_4$, 4 h
11	**1f**	**2f** (76)		TfOH, 4 h
				
12	**1g**, R = Br	**2g** (52)	**2g'** (24)	$SnCl_4$, 4 h
13	**1g**, R = Br	**2g** (31)	**2g'** (24)	$TiCl_4$, 4 h
14	**1g**, R = Br	**2g** (35)	**2g'** (11)	TfOH, 4 h
15	**1h**, R = Cl	**2h** (42)	**2h'** (16)	$SnCl_4$, 4 h
16	**1h**, R = Cl	**2h** (44)	**2h'** (25)	$TiCl_4$, 4 h
17	**1h**, R = Cl	**2h** (52)	**2h'** (6)	TfOH, 4 h
				
18	**1i**	**2i** (34)		$SnCl_4$, 4 h
19	**1i**	**2i** (57)		$TiCl_4$, 4 h
				
20	**1j**	**2j** (71)		$SnCl_4$, 4 h
21	**1j**	**2j** (64)		$TiCl_4$, 4 h

[a]Treatment of azido acid **1** with $(COCl)_2$ in DCM for 1 h at room temperature followed by acid promoter (4 equiv) in refluxing DCM for the time mentioned in the table. [b]Isolated yield. [c]Refluxing period of the reaction.

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(Table 1, entry 20). Finally, the structure of lactam **2j** was confirmed unambiguously by X-ray crystallographic analysis (Figure 1).

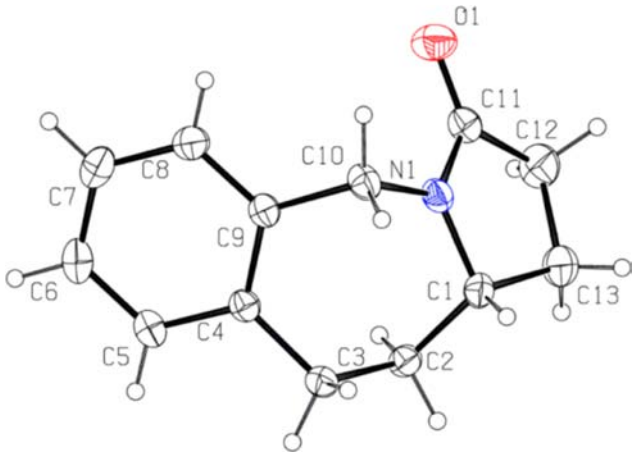

Figure 1. X-ray structure of lactam **2j**.

The above experiments suggested the formation of *N*-acyliminium ions in the process, which were derived from the aminodiazonium ion species. Given the wide application of *N*-acyliminium ion in construction of carbon−carbon and carbon−heteroatom bonds,[11] the Schmidt reaction of acyl chlorides with alkyl azides through *N*-acyliminium ion intermediates would be of high potential importance in synthetic chemistry.

In conclusion, we have designed and realized the Schmidt reaction of acyl chlorides with alkyl azides through *N*-acyliminium ion intermediates. An efficient one-pot, three-step protocol combining acyl chlorination, intramolecular Schmidt reaction of the acyl chloride, and Pictet−Spengler cyclization of the *N*-acyliminium ion intermediate are achieved to afford several different types of nitrogen-containing tricyclic skeletons in good yield.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data and copies of NMR spectra for all new compounds and X-ray crystallographic data for compound **2j**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gupm@nxu.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For two recently selected reviews on Schmidt reaction of carboxylic acids with HN_3, see: (a) Wrobleski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1−320. (b) Aubé, J. In *Organic Azides: Synthesis and Applications*; Brase, S., Banert, K., Eds.; Wiley: Weinheim, 2010; pp 191−237.

(2) For the Schmidt reaction of aldehydes with alkyl azides, see: (a) Lee, H.-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007−9015. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449−10459.

(3) For the modified intermolecular Schmidt reaction of aldehydes with azido alcohols, see: (a) Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484−2487. (b) Boyer, J. H.; Morgan, L. R., Jr. *J. Org. Chem.* **1959**, *24*, 561−562. (c) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325−327. (d) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951−954.

(4) For the modified intermolecular Schmidt reaction of aldehydes with an azido amine developed in our group, see: Gu, P.; Sun, J.; Kang, X.-Y.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. *Org. Lett.* **2013**, *15*, 1124−1127.

(5) For the represent Schmidt reaction ketones of with alkyl azides, see: (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965−8966. (b) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635−1637.

(6) For the Schmidt reaction of carbocations with alkyl azides, see: (a) Pearson, W. H.; Schkeryantz, J. M. *Tetrahedron Lett.* **1992**, *33*, 5291−5294. (b) Pearson, W. H.; Walavalkar, R.; Schkeryantz, J. M.; Fang, W.; Blickensdorf, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 10183−10194. (c) Reddy, P. G.; Varghese, B.; Baskaran, S. *Org. Lett.* **2003**, *5*, 583−585.

(7) Gu, P.; Kang, X.-Y.; Sun, J.; Wang, B.-J.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. *Org. Lett.* **2012**, *14*, 5796−5799.

(8) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771−3774.

(9) Known compound: (a) Song, L.; Liu, K.; Li, C. *Org. Lett.* **2011**, *13*, 3434−3437. (b) Clark, A. J.; Filika, R. P.; Peacocka, J. L.; Thomas, G. H. *Synlett* **1999**, 441−443.

(10) For a selected review on the Pictet−Spengler reaction, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842.

(11) For a selected review on the cyclizations of *N*-acyliminium ions, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431−1628.