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Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides: Rapid Access to Fused Polycyclic Nitrogen-Containing Heterocycles via a Multistep One-Pot Transformation

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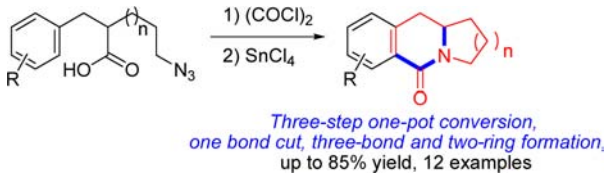
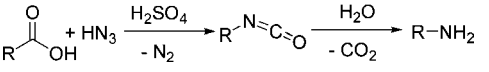
ABSTRACT



The first intramolecular Schmidt reaction of acyl chlorides with alkyl azides has been developed. In this one-pot conversion, an ω-azido hydrocinnamic acid is converted to a tricyclic lactam. The most important feature of the process is the efficiency in bond formation (one bond broken and three new bonds created) and ring construction (two new rings formed).

The Schmidt reaction of carboxylic acids with hydrazoic acid (HN_3) in the presence of acid catalysts was reported to afford amines,[1] which were one-carbon shorter homologues of the substrates (Scheme 1). The replacement of HN_3 with an alkyl azide for the analogous conversion of ketones[2] or carbocations[3] was realized by Aubé and by Pearson in the early 1990s. Since then, the intramolecular Schmidt reaction has proven to be a powerful strategy for the synthesis of natural and non-natural products.[4] However no successful conversion of carboxylic acids or their derivatives with alkyl azides has been reported. In this paper, we describe the first efficient intramolecular reaction of alkyl azides with acyl chlorides to give fused polycyclic nitrogen-containing heterocycles.

Scheme 1. Schmidt Reaction of Carboxylic Acid with HN_3



The isocyanate intermediate in the classical Schmidt reaction of carboxylic acid with HN_3 was hydrolyzed by water, with subsequent release of carbon dioxide. We envisioned that an isocyanate ion would be formed if the alkyl azides were reacted with a carboxylic acid (Scheme 2). To increase the atom efficiency of this conversion, the intramolecular capture of the promised intermediate was

(1) For selected reviews on the Schmidt reaction of carboxylic acids with HN_3, see: (a) Wolff, H. *Org. React.* **1946**, *3*, 307–336. (b) Koldobskii, G. I.; Ostrovskii, V. A.; Gidaspov, B. V. *Russ. Chem. Rev.* **1978**, *47*, 1084–1094. (c) Shioiri, T. *Comp. Org. Synth.* **1991**, *6*, 795–828. (d) Wrobleski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1–320.

(2) (a) Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. (b) Milligan, G. L.; Mossman, C. J.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459.

(3) (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.

(4) For a selected review, see: Aubé, J. In *Organic Azides: Synthesis and Applications*; Brase, S., Banert, K., Eds.; Wiley: Weinheim, 2009; pp 191–237.

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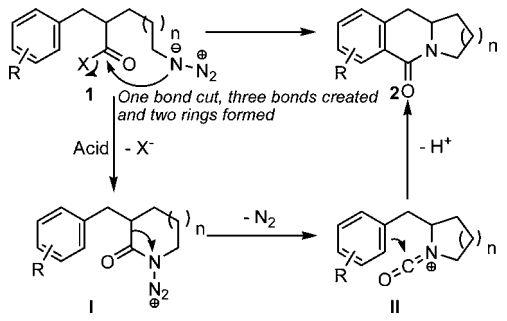
designed. The azido carboxylic acid or its derivative **1** was selected for this attempt. The process would be initiated by the intramolecular nucleophilic attack of the azido group upon the carbonyl group of acid or its derivative, which would result in forming the aminodiazonium ion intermediate **I** under acidic conditions. The 1,2-migration of the C−C bond attaching to the carbonyl group to the nitrogen atom would give the isocyanate ion **II**, which would be captured by the aromatic ring[5] to afford lactam **2**. The aromatic ring was selected for nucleophilic addition due to the potential synthetic application of the product, which is a prominent substructure in many alkaloids.

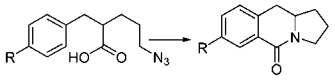
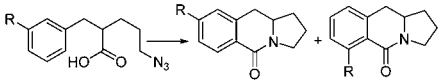
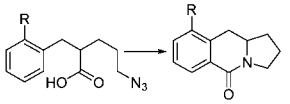
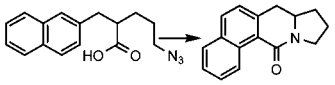
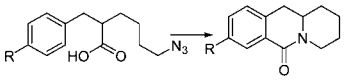
Scheme 2. Design of Intramolecular Schmidt Reaction of Carboxylic Acid Derivatives with Alkyl Azides



To test our proposal, the azido acid **1a** was prepared by hydrolysis of the corresponding ester.[6] Treatment of **1a** with $SnCl_4$ (4.0 equiv) for 17 h in refluxing DCM failed to give any of the desired lactam **2a**. To our delight, activation of the azido acid with $(COCl)_2$ (3.5 equiv) in the presence of a catalytic amount of DMF followed by the addition of $SnCl_4$ gave the lactam **2a** in 85% yield (entry 1, Table 1).[7] We reasoned that the acyl chloride formed in situ was more reactive than the carboxylic acid **1a** during the nuclephilic attack of the azido group.

After the successful conversion of **1a** to the lactam **2a**, a series of azido acids **1b**−**1l** were all smoothly converted to the corresponding lactams. The structures of **2b** and **2j** were confirmed by X-ray crystallographic analysis.

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

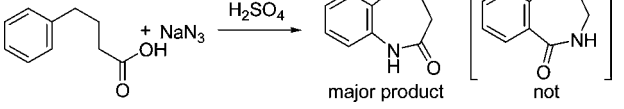
entry	azides	products (yield[b])	time[c] (h)
			
1	**1a** R = H	**2a** (85%)	4
2	**1b** R = Me	**2b** (77%)	4
3	**1c** R = OMe	**2c** (68%)	4
4	**1d** R = Cl	**2d** (63%)	18
5	**1e** R = Br	**2e** (61%)	16
			
6	**1f** R = OMe	**2f** (30%) **2f'** (20%)	16
7	**1g** R = Br	**2g** (54%) **2g'** (13%)	24
			
8	**1h** R = Cl	**2h** (81%)	23
9	**1i** R = Br	**2i** (78%)	23
			
10	**1j**	**2j** (84%)	23
			
11	**1k** R = H	**2k** (40%)	22
12	**1l** R = Cl	**2l** (67%)	23

[a] Treatment of azido acid **1** with $(COCl)_2$ in the presence or absence of DMF in DCM for 1 h at room temperature followed by $SnCl_4$ (4 equiv) in refluxing DCM for the time mentioned in the table. [b] Isolated yield. [c] Refluxing period of the reaction.

Noteworthy features of the conversion include the following: (1) elegant efficiency of the process has been demonstrated in bond formation (three new bonds created) and ring construction (two new rings); (2) the reaction proceeds through a three-step sequence, acylchlorination of the carboxylic acid, Schmidt rearrangement of the acyl chloride with the alkyl azide, and electrophilic addition of the isocyanate ion to the aromatic ring; (3) the overall yields of this conversion are good, even for the preparation of lactam **2k**, with the average yield of the three steps being 74% from the overall 40% yield (entry 11); (4) the steric effect of ortho substituents is minimal (entries 8 and 9); (5) electron-withdrawing or -donating groups on the aromatic ring exhibit comparable reactivity in the preparation of benzoindolizidine units (entries 1−10); (6) an electron-withdrawing group gives a better result in the synthesis of benzoquinuolizidine units (entries 11 and 12); (7) the meta-substituted aromatic rings result in lactams in the mixture of regioisomers (entries 6, 7) while the 2-naphthyl analogue affords only one lactam, **2j** (entry 10).

The azido aromatic ketones **5f** and **5f'** (Scheme 3) were separated as minor products from the reaction mixture, from the competitive intramolecular Friedel−Crafts acylation

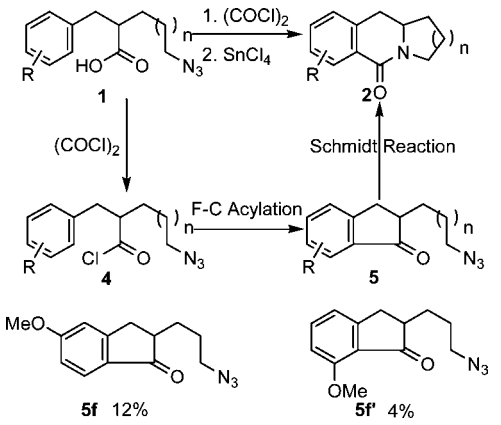
(5) Previous conversion of 4-phenylbutyric acid with HN_3 in the presence of sulfinic acid afforded cyclic amide, which was different in form from the products in this paper; see: Datta, S. K.; Grundmann, C.; Bhattacharyya, N. K. *J. Chem. Soc. (C)* **1970**, 2058.



(6) Lee, H.-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007–9015.

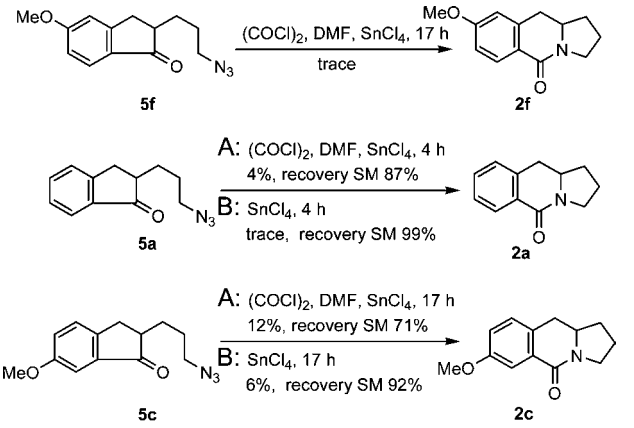
(7) Known compound; for selected papers, see: (a) Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035–1038. (b) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933–4940. (c) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951–5958. (d) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851–8860. (e) Brenzovich, W. E., Jr.; Benitez, D.; Lackner, A. D.; Shunatona, H. P.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5519–5522. (f) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157–12159.

Scheme 3. A Possible Process of Acyl-Chlorination/Friedel–Crafts Acylation/Schmidt Reaction to Address Lactam from Azido Acid



by the acyl chloride of the aromatic ring. These ketones raised the possibility that the lactams **2** are the product of a domino process of intramolecular Friedel–Crafts acylation/intramolecular Schmidt reaction.[8] However, azido aromatic ketones had been proven to be less reactive than their analogue of azido aliphic ketones.[2b] The aromatic ketone **5f** was therefore submitted to the reaction conditions but failed to give the lactam **2f** (Scheme 4). Furthermore, we had prepared the azido ketones **5a** and **5c** (see Supporting Information for details), which were possible intermediates toward the lactams **2a** and **2c** by the competing mechanism. Treatment of **5a** with $SnCl_4$ in the presence or absence of $(COCl)_2$ with a catalytic amount of DMF for 4 h gave only a trace of lactam **2c**. The ketone **5c** was exposed to the reaction conditions for an even longer time (17 vs 4 h) and still failed to give the lactam **2c** in reasonable yield. It should be noted that the two competing processes (Schemes 2 and 3) are both initiated from the acyl chloride. Once the acyl chloride was formed, the competition between the intramolecular nucleophilic attack of the azide upon the acyl chloride (the first process) with Friedel–Crafts acylation (the second process) would take place. If Friedel–Crafts acylation were faster, the aromatic ketone would be formed and should have survived, as the Schmidt reaction of the aromatic ketone is clearly not favored. We conclude that the polycyclic lactams were mainly delivered from the Schmidt reaction of the acyl chlorides with the alkyl azides.

Scheme 4. Attempt to Convert the Azido Aromatic Ketones to Lactams



The successful conversion of azido acyl chlorides offers a reliable method to address benzo fused lactams, which are difficult to obtain from the Schmidt reaction of aromatic ketones. It should be noted that the lactams in Table 1 represented benzoindolizidine and benzoquinuolizidine units, which widely exist in phenanthropiperidine alkaloids[9] and *Amaryllidaceae* alkaloids.[10]

In conclusion, we have established a practical procedure for the construction of fused polycyclic nitrogen-containing heterocycles. The three-step combination of acyl chlorination, Schmidt reaction of the acyl chloride, and electrophilic addition of the isocyanate ion onto the aromatic ring in one pot gives the polycyclic lactams in good yield. The most important feature of the process is the efficiency in bond formation and ring construction. The competitive mechanism of the conversion through a domino process of intramolecular Friedel–Crafts acylation/intramolecular Schmidt reaction was excluded by further experiments. Currently, extensive applications of this methodology in the total synthesis of natural products are underway in our laboratory.

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(8) For domino processes involving an intramolecular Schmidt reaction of ketones, see: (a) Golden, J. E.; Aubé, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4316–4318. (b) Zeng, Y.; Reddy, D. S.; Hirt, E.; Aubé, J. *Org. Lett.* **2004**, *6*, 4993–4995. (c) Zeng, Y.; Aubé, J. *J. Am. Chem. Soc.* **2005**, *127*, 15712–15713. (d) Gu, P.; Zhao, Y.-M.; Tu, Y. Q.; Ma, Y.; Zhang, F. *Org. Lett.* **2006**, *8*, 5271–5273. (e) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018–6024. (f) Zhao, Y.-M.; Gu, P.; Tu, Y.-Q.; Fan, C.-A.; Zhang, Q. *Org. Lett.* **2008**, *10*, 1763–1766. (g) Huh, C. W.; Somal, G. K.; Katz, C. E.; Pei, H.; Zeng, Y.; Douglas, J. T.; Aubé, J. *J. Org. Chem.* **2009**, *74*, 7618–7626. (h) Meyer, A. M.; Katz, C. E.; Li, S.-W.; Velde, D. V.; Aubé, J. *Org. Lett.* **2010**, *12*, 1244–1247. (i) Chen, Z.-H.; Tu, Y.-Q.; Zhang, S.-Y.; Zhang, F.-M. *Org. Lett.* **2011**, *13*, 724–727. (j) Huh, C. W.; Schroeder, C.; Singh, G.; Aubé, J. *J. Org. Chem.* **2011**, *76*, 3160–3165.

(9) Reviews: (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, *16*, 2365–2378. (b) Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50–73. (c) Bick, I. R. C.; Sinchai, W. *The Alkaloids* **1982**, *19*, 193–220. (d) Govindachari, T. R.; Viswanathan, N. *Heterocycles* **1978**, *11*, 587–613.

(10) For reviews on *Amaryllidaceae* alkaloids, see: (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 363–381 and previous reviews in this series. (b) Hoshino, O. *The Alkaloids* **1998**, *51*, 323–424. (c) Martin, S. F. *The Alkaloids* **1988**, *30*, 251–376.

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

The authors declare no competing financial interest.