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An Intramolecular Schmidt Reaction of δ-Azido *N*-Acylbenzotriazoles

Chun-Fang Liu,‡ Zhi-Qi Cao,‡ Shao-Lei Ding, Jing Zhu, and Peiming Gu*

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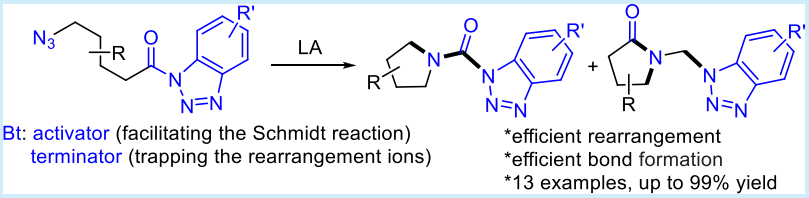

ABSTRACT: A Lewis acid promoted intramolecular Schmidt reaction of *N*-acylbenzotriazoles with alkyl azides was designed and realized. The benzotriazole was not only employed as an efficient activator for initiating the Schmidt rearrangement but also used as a powerful terminator for the subsequent nucleophilic trapping of the isocyanate ion and/or *N*-acyliminium ion from the rearrangement. Thirteen δ-azido *N*-acylbenzotriazoles were investigated, and the conversion afforded the desired benzotriazole-1-carboxamides and lactams with good to excellent yields.

The classic Schmidt reaction of HN_3 with aldehydes, ketones, and carboxylic acids is a powerful approach for accessing to the nitrogen-containing molecules,[1] and in the past three decades, efforts in replacement of the highly toxic HN_3 with other nitrogen reactants have made great success,[1c,2,3] resulting in more efficient aza-ring formation. The less reactive alkyl azides were systematically demonstrated as successful azides in reaction with ketones and aldehydes by Aubé's group,[4] and then the electrophiles were expanded to the carbenium ions derived from alkenes[5] or alcohols[5a,6] or expoxides[7] or alkynes;[8] however, the carboxylic acids were unreactive with the alkyl azides. We have realized the Schmidt reaction of alkyl azides with the carboxylic acids via an *in situ* activation strategy for the carboxylic acids,[9] where isocyanate ion and *N*-acyliminium ion salts were proposed as the initial products. The two ions could be terminated by an additional nucleophile to produce electroneutral products (Scheme 1), but only the major ion could be captured by the preinstalled intramolecular nucleophile, and trapping the minor ion should fail as the potential product is the unfavored bridged lactam. Intermolecular capture of the two rearrangement ions with excessive doses of nucleophiles could be a reasonable choice, though it gave only poor results.[10] In seeking to explore the more efficient activation strategies for the carboxylic acids and new electrophiles for the Schmidt reaction, we report here an intramolecular reaction of the alkyl azides with the *N*-acylbenzotriazoles.

Investigation of the amide as an electrophile for the Schmidt reaction of alkyl azides would be desirable, although the amide presents a challenge as it is generally a less reactive substrate, mainly due to the p−π conjugation in the amide group. According to our previous research, for the Schmidt reaction of alkyl azides with carboxylic acid derivatives to be feasible, two major issues might be addressed: (1) a good leaving group should be attached to the carbonyl group for better initiating the rearrangement and (2) a suitable nucleophile is required for efficiently capturing the isocyanate ion or *N*-acyliminium ion from the Schmidt reaction.

The benzotriazole is regarded as an excellent leaving group in synthetic chemistry, and it has been extensively applied in many organic transformations.[11] Therefore, 1-acylbenzotriazole,[12] also a type of amide, could be a potential electrophile for the intramolecular Schmidt reaction of alkyl azides. It was envisioned that nucleophilic attack of azide onto the 1-acylbenzotriazole would take place when the δ-azido *N*-acylbenzotriazole **1** was activated by an acid promoter (Scheme 2), and an acyl *N*-diazonium ion intermediate **I** would be generated with releasing a benzotriazole anion. Then the isocyanate ion **II** and *N*-acyliminium ion **III** would be produced from the rearrangement of intermediate **I**, where the competitive 1,2-shift of two β-carbons to the electron-deficient nitrogen atom with loss of nitrogen gas would proceed. Finally, both the isocyanate ion **II** and *N*-acyliminium ion **III** would be *in situ* intermolecularly captured by the strongly nucleophilic benzotriazole anion, and the benzotriazole type carbamide **2** and lactam **3** would be furnished as the ultimate products.

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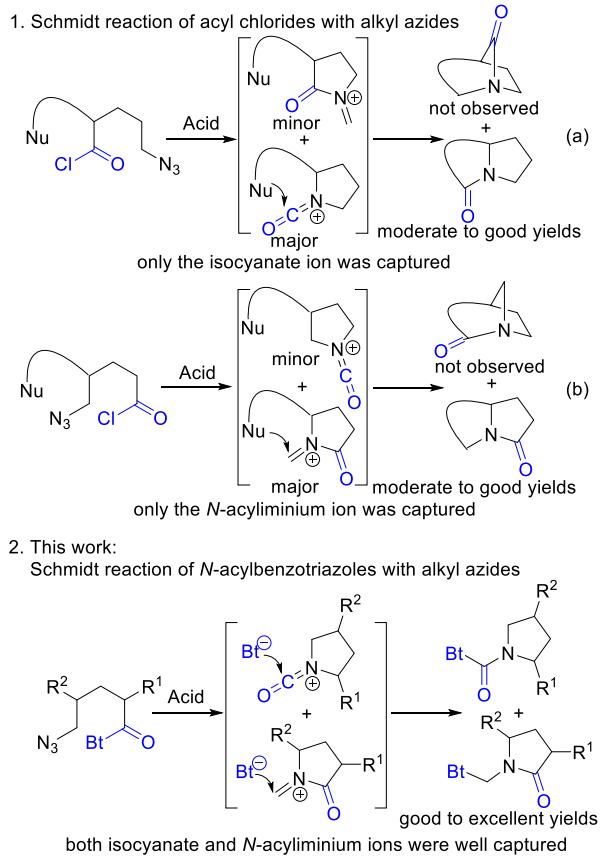
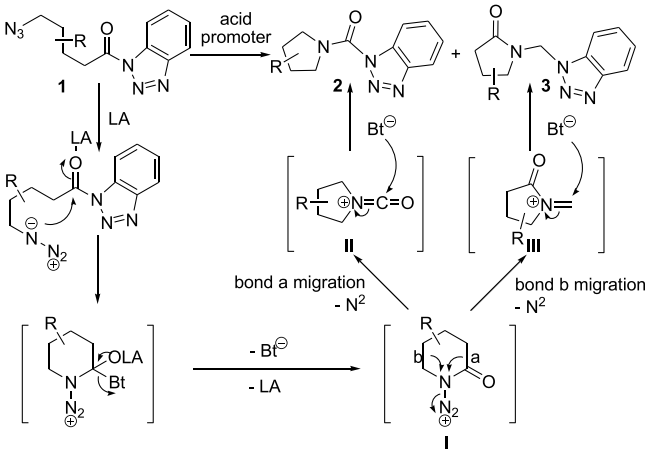
Scheme 1. Schmidt Reaction of Alkyl Azides with Carboxylic Acid Derivatives

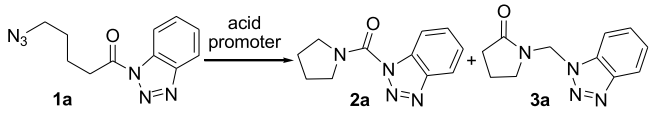


Scheme 2. Proposed Process for the Schmidt Reaction of Alkyl Azides with *N*-Acylbenzotriazoles



The δ-azido *N*-acylbenzotriazole **1a**[13] was prepared for testing the above hypothesis, and several acids (3.0 equiv) were applied to promote the reaction in the refluxing dichloromethane (Table 1). Among the acid promoters, $BF_3{\cdot}OEt_2$ was found to be a promising one, and the carbamide **2a** with a yield of 17% and the lactam **3a** with a yield of 20% were isolated after 24 h, where 30% of **1a** could be recovered. To consume all of the substrate, the reaction temperature was increased, and the conversion was carried out in refluxing dichloroethane. As expected, both of the rearrangement ions were well captured with the benzotriazole anion, and the

Table 1. Schmidt Reaction of the δ-Azido *N*-Acylbenzotriazole 1a[a]



entry	acid	conditions	results (yield,[b] %)
1	$SnCl_4$	reflux, DCM, 24 h	dec[c]
2	$TiCl_4$	reflux, DCM, 24 h	**2a** (10), **3a** (20)
3	Et_2AlCl_2	reflux, DCM, 24 h	dec[c]
4	$BF_3{\cdot}OEt_2$	reflux, DCM, 24 h	**2a** (17), **3a** (20)
5	TfOH	reflux, DCM, 24 h	complex, **3a** (8)
6	TFA[d]	rt, 24 h	dec[c]
7	$BF_3{\cdot}OEt_2$	reflux, DCE, 2.5 h	**2a** (45), **3a** (45)
8[e]	$BF_3{\cdot}OEt_2$	reflux, DCE, 3.5 h	**2a** (45), **3a** (34)
9	$BF_3{\cdot}OEt_2$	reflux, DCE, 4 h	**2a** (34), **3a** (38)
10	$SnCl_4$	reflux, DCE, 120 h	complex, **3a** (25)
11	$TiCl_4$	reflux, DCE, 120 h	complex, **3a** (18)
12[f]	$BF_3{\cdot}OEt_2$	reflux, DCE, 4 h	**2a** (45), **3a** (43)

[a]Reaction of the δ-azido *N*-acylbenzotriazole **1a** (73 mg, 0.30 mmol) with the acid promoter (0.90 mmol) in the mentioned solvent (1.5 mL). [b]Isolated yield. [c]Hydrolysis of the *N*-acylbenzotriazole was observed. [d]TFA (1.5 mL) as the reaction solvent. [e]Reaction promoted with 0.60 mmol of $BF_3{\cdot}OEt_2$. [f]Reaction with 1.0 mmol of **1a**.

desired carbamide **2a** and lactam **3a** were obtained in a combined yield of 90% with a ratio of 1/1 in 2.5 h (entry 7, Table 1). The carbamide **2a** was further characterized by X-ray single-crystal diffraction. Then the attempt to reduce the acid promoter (2.0 equiv) encountered a failure, and the combined yield of the desired products was reduced to 79% (entry 8, Table 1). It should be noted that a longer reaction time would count against the yield, and benzotriazole was significantly produced (entry 9, Table 1). Then the carbamide **2a** and lactam **3a** were isolated and subjected to $BF_3{\cdot}OEt_2$ at refluxing dichloroethane for 3 h, and the carbamide **2a** was completely decomposed to benzotriazole, while only trace benzotriazole was observed with that of lactam **3a**. Further, $SnCl_4$ and $TiCl_4$ were re-examined for the Schmidt reaction of **1a** in refluxing dichloroethane; however both reactions failed to give positive results, and the substrate was consumed after 120 h, affording the lactam **3a** with poor yields from the very complex reaction mixtures (entries 10 and 11, Table 1).

The potential migratory groups in the rearrangement of **1a** were two methylene carbons, and the above results indicated that the shift process had poor regioselectivities. Then an alkyl or an aryl group was assembled at the α-carbon of the carbonyl group, and the δ-azido *N*-acylbenzotriazoles **1b**−**1f** were prepared for exploration. With the optimized reaction conditions in hand (entry 7, Table 1), substrates **1b**−**1f** were all converted to the desired carbamides and lactams with excellent combined yields (Scheme 3). Reaction of azide **1b** for 25 min afforded the benzotriazole-1-carboxamide **2b** with 79% yield and the lactam **3b** with 11% yield, and it was observed that 68% of **2c** and 22% of **3c** were obtained from the reaction of substrate **1c**, suggesting steric hindrance might slightly affect the migration process. It seemed that a shift of the benzylic methine carbon was more preferred, where the reaction of acylbenzotriazoles **1d** gave a carbamide **2d** with 93% yield and the lactam **3d** with only 6% yield. However, the substrate **1e** attached with a chlorine at the para position of the aryl ring in the benzylic substrate led to slightly decreased regioselectivitiy,

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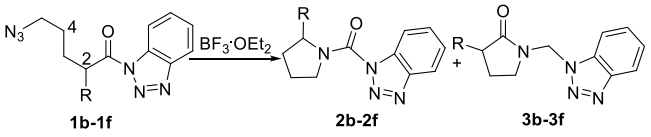
Scheme 3. Schmidt Reaction of the 2-Substituted δ-Azido *N*-Acylbenzotriazoles 1b−1f



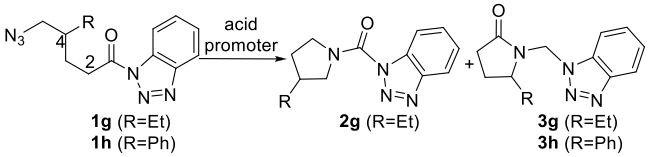
1b: R = C_2H_5	25 min[a]	**2b** (79%), **3b** (11%)
1c: R = C_7H_{15}	30 min[a]	**2c** (68%), **3c** (22%)
1d: R = C_6H_5	2.5 h[a]	**2d** (93%), **3d** (6%)
1e: R = *p*-Cl-C_6H_4	3.0 h[a]	**2e** (74%), **3e** (16%)
1f: R = *p*-Me-C_6H_4	2.0 h[a]	**2f** (63%), **3f** (trace)
1f	5.7 h[b]	**2f** (89%), **3f** (trace)

[a]Reaction of the δ-azido *N*-acylbenzotriazole **1** (0.30 mmol) with BF_3·OEt_2 (0.90 mmol) in the refluxing dichloroethane (1.5 mL). [b]Reaction of **1f** (100 mg, 0.30 mmol) with BF_3·OEt_2 (47 mg, 42 μL, 0.33 mmol) in refluxing dichloroethane (1.5 mL).

where the carbamide **2e** was obtained in 74% and lactam **3e** was isolated in 16% yield. The δ-azido *N*-acylbenzotriazole **1f** was converted into the carbamide **2f** in 63% yield with the above reaction conditions; meanwhile, trace **3f** could be observed and obvious decomposition of the products occurred with this case. Then the substrate **1f** was treated with less BF_3·OEt_2 (1.1 equiv) for 5.7 h in the refluxing dichloroethane, and fortunately, the yield of carbamide **2f** was improved to 89%. With these types of substrates, the carbamides **2** from migration of the methine carbon (C2) were all obtained as the dominant products, and the lactams **3** from migration of the methylene carbon (C4) were isolated as the minor products.

The δ-azido *N*-acylbenzotriazole **1g**, in the form of **1a** attached by an ethyl group at the C4 position, had two different types of β-carbons for the potential migration. Compound **1g** as treated with BF_3·OEt_2 for 25 min, and the carbamide **2g** from migration of a methylene carbon (C2) was observed with 16% yield as a minor product and the lactam **3g** from the competitive migration of a methine carbon (C4) was isolated with 77% yield (Scheme 4). Interestingly, treatment of

Scheme 4. Schmidt Reaction of 4-Substituted δ-Azido *N*-Acylbenzotriazoles 1g and 1h

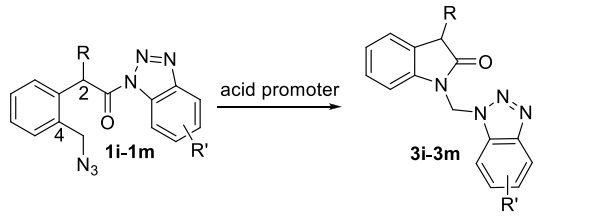


BF_3·OEt_2 (3.0 equiv), 25 min in refluxing DCE,	**2g** (16%), **3g** (77%)
$SnCl_4$ (2.0 equiv), 3.0 h at 60 °C in DCE,	**2g** (30%), **3g** (68%)
BF_3·OEt_2 (3.0 equiv), 25 min in refluxing DCE,	**3h** (90%)

1g with $SnCl_4$ (2.0 equiv) at 60 °C in dichloroethane for 3 h afforded **2g** (30%) and **3g** (68%) with a higher combined yield of 98%. It indicated that the migratory aptitudes of the two β-carbons could be slightly influenced by the acid promoters, as more **2g** was obtained with the $SnCl_4$-promoted reaction when compared with that of BF_3·OEt_2-promoted reaction. When the 4-phenyl δ-azido *N*-acylbenzotriazole **1h** was treated with BF_3·OEt_2, only the lactam **3h** could be observed and isolated in 90% yield from the reaction mixture, indicating that migration of C-4 significantly increased when the phenyl ring was attached at the shifting group.

Generally, migration of the aryl group was favored over the alkyl group in the Schmidt reaction (Scheme 5). To enhance

Scheme 5. Schmidt Reaction of δ-Azido *N*-Acylbenzotriazole 1i−1m



1i: R = H, R' = H	BF_3·OEt_2 (3.0 equiv), refluxing DCE, 3h	**3i** (12%)
	$SnCl_4$ (2.0 equiv), 60 °C in DCE, 5h	**3i** (87%)
	TfOH (2.0 equiv), rt in DCE, 50 min	**3i** (90%)
1j: R = C_2H_5, R' = H	$SnCl_4$ (2.0 equiv), 60 °C in DCE, 8.5h	**3j** (81%)
1k: R = Bn, R' = H	$SnCl_4$ (2.0 equiv), 60 °C in DCE, 8.5h	**3k** (82%)
	TfOH (2.0 equiv), rt in DCE, 20 min	**3k** (46%)
1l: R = H, R' = Me	$SnCl_4$ (2.0 equiv), 60 °C in DCE, 12h	**3l** (87%)
1m: R = Et, R' = Me	$SnCl_4$ (2.0 equiv), 60 °C in DCE, 5h	**3m** (86%)

the migration of C4, five more substrates **1i−1m** were prepared for investigation. BF_3·OEt_2 was not a good promoter for the reaction of these substrates, where only 12% of 2-oxoindole **3i** could be isolated from the BF_3·OEt_2-promoted reaction of **1i**. It should be noted that the benzotriazole type product was unstable under the acidic conditions, and the low yield could be owing to the decomposition of **3i**. Fortunately, further evaluation revealed that $SnCl_4$ and TfOH could give better results for the reaction of azide **1i**, and only migration of the aryl group was observed, affording **3i** from the *N*-acyliminium ion as the sole product with 87% and 90% yields, respectively. Further, the structure of oxoindole **3i** was confirmed unambiguously by X-ray diffraction single-crystal structural analysis. Then $SnCl_4$ was employed as the acid promoter for this type of substrate. 2-Oxoindoles **3j** and **3k** were produced with 81% and 82% yields from the substrates **1j** and **1k**, and again the competitive shift of the benzylic methine carbon was entirely restricted. TfOH was not reliable when it was employed for the reaction of the δ-azido *N*-acylbenzotriazole **1k**, where the desired **3k** was isolated in only 46% yield from the complex reaction mixture. Azides **1l** and **1m** with a methyl benzotriazole unit were also converted into the desired oxoindoles **3l** and **3m** with $SnCl_4$ in both good yields.

Finally, a mixture of **1j** and **1l** was treated with $SnCl_4$ at 60 °C for 6 h in dichloroethane (Scheme 6), and the oxoindoles **3i**, **3j**, **3l**, and **3m** were obtained in a combined yield of 67%, where the ratio of the four oxoindoles was determined by ^1H NMR as about 1:1:1:1. Formation of oxoindoles **3i** and **3m** from the cross experiment supported the proposed reaction process, where the benzotriazole anion was released at the rearrangement stage and the *N*-acyliminium ion was intermolecularly captured by the benzotriazole anion in termination stage.

The Bt group could be removed from the rearrangement product, and two experiments were carried out on the carbamide **2d** (Scheme 7). Treatment of **2d** with $TiCl_4$ gave lactam **5d** in 56% yield, where an intramolecular Friedel−Crafts-type acylation occurred. The carbamide **2d** could also be reduced by sodium borohydride, furnishing a formamide **6d** in 81% yield.

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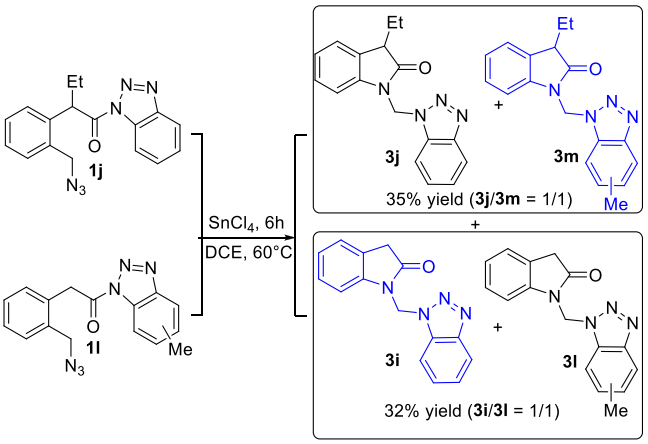
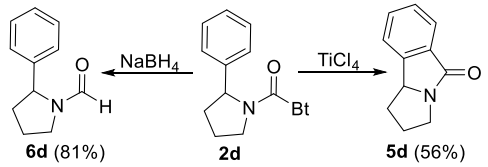
Scheme 6. Cross Reaction of 1j and 1l



Scheme 7. Conversion of Carbamide 2d



In summary, the benzotriazole-activated intramolecular Schmidt reaction of the ω-azido carboxylic acids was designed, and it proceeded efficiently. Generally, the initial products from the rearrangement reaction, isocyanate ion, and/or *N*-acyliminium ion were produced in the presence of acid promoter, and then they were rapidly captured by the benzotriazole anion. Thirteen ω-Azido *N*-acylbenzotriazoles were successfully converted into the corresponding carbamides **2** and/or lactams **3** in good to excellent combined yields, and the ratio of the products reflected the competitive 1,2-migration of two β-carbons to the nitrogen atom.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. Experimental procedures and spectra for all new compounds (PDF) X-ray crystallographic data for **2a** and **3i** (CIF) The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00200.

Experimental procedures and spectra for all new compounds (PDF)

Accession Codes

CCDC 1976207−1976208 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Peiming Gu − *College of Chemistry & Chemical Engineering, Ningxia Engineering and Research Center for Natural Medicines, Ningxia University, Yinchuan 750021, China;* orcid.org/0000-0002-2812-4019; Email: gupm@nxu.edu.cn

Authors

Chun-Fang Liu − *College of Chemistry & Chemical Engineering, Ningxia Engineering and Research Center for Natural Medicines, Ningxia University, Yinchuan 750021, China*

Zhi-Qi Cao − *College of Chemistry & Chemical Engineering, Ningxia Engineering and Research Center for Natural Medicines, Ningxia University, Yinchuan 750021, China*

Shao-Lei Ding − *College of Chemistry & Chemical Engineering, Ningxia Engineering and Research Center for Natural Medicines, Ningxia University, Yinchuan 750021, China*

Jing Zhu − *College of Chemistry & Chemical Engineering, Ningxia Engineering and Research Center for Natural Medicines, Ningxia University, Yinchuan 750021, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00200

Author Contributions

‡C.-F.L. and Z.Q.C. contributed equally.

Notes

The authors declare no competing financial interest.

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(13) Caution: the azides are suggested to be potentially explosive compounds, and care should be taken in its handling.

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