



## Intermolecular Schmidt reaction of alkyl azides with acyl silanes



Chun-Jiao Yu, Rui Li\*, Peiming Gu

School of Chemistry & Chemical Engineering, Ningxia Engineering and Research Center for Natural Medicines, Ningxia University, Yinchuan 750021, China

### ARTICLE INFO

#### Article history:

Received 22 May 2016

Revised 24 June 2016

Accepted 27 June 2016

Available online 28 June 2016

#### Keywords:

Schmidt reaction

Acyl silanes

Alkyl azides

Amides

Rearrangement

### ABSTRACT

The first intermolecular Schmidt reaction of alkyl azides with acyl silanes has been designed and realized, producing a range of amides with absolute site selectivity in good to excellent yields. The mechanism of the conversion has been proposed, and the reaction exhibits scope of substrates.

© 2016 Elsevier Ltd. All rights reserved.

The classic Schmidt rearrangement involves the acid-promoted reaction of hydrazoic acid ( $\text{HN}_3$ ) and electrophiles.<sup>1</sup> A variety of electrophiles including aldehydes, ketones, carbenium ions from alkenes or alcohols, and acylium ions from carboxylic acids, are used for the conversion, producing several different types of *N*-containing products. Soon after, replacement of  $\text{HN}_3$  with the more weakly nucleophilic alkyl azides has become a hot research topic with the Schmidt reaction. The alkyl azides have proven to be very successful for the intramolecular Schmidt reaction, while the intermolecular reaction is comparatively less efficient. In the early stage, the electrophiles for the Schmidt reaction of alkyl azides were mainly restricted to aldehydes, ketones, and carbenium ions. Investigation on new electrophiles for this reaction should be academically desirable and interesting. Toste and co-workers had reported the Au(I)-catalyzed intramolecular Schmidt reactions of acetylenic azides.<sup>2</sup> Very recently, our group had demonstrated that the acyl chlorides were suitable for the intramolecular Schmidt reaction of alkyl azides.<sup>3</sup> Herein, we reported the extension of electrophiles to acyl silanes for the intermolecular Schmidt reaction of alkyl azides, efficiently affording amides with absolute site selectivity.

Generally, the intermolecular Schmidt reaction of alkyl azides suffers from poor yields (Scheme 1). Aldehydes, very reactive carbonyl compounds, had been examined with the alkyl azides under protic acid conditions, and the best yield was only 25%.<sup>4</sup> Lewis acids had been used to enhance the efficiency of the conversion, but the yield was still moderate and the reaction was poorly site

selective.<sup>5</sup> Generally, the analogy intermolecular insertion of alkyl azides with ketones with less efficiency was observed, and the reaction was very sensitive to substrates.<sup>6</sup> Further, the conceptually intermolecular Schmidt reaction could be highly efficient when the alkyl azide was replaced by an azido alkanol<sup>4b,7</sup> or an azido alkylamine,<sup>8</sup> where the intermolecular reaction was in fact changed to an intramolecular one before the Schmidt rearrangement. It should be noted that the amidation of aldehydes with azides was recently developed through the strong base promoted process<sup>9</sup> or the transition metal catalyzed conversion,<sup>10</sup> however the conversion suffered from very severe substrate limitation.

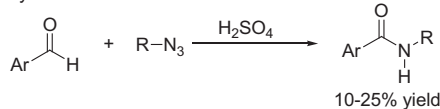
For the Schmidt reaction of alkyl azides with aldehydes, the initial nucleophilic attack of an alkyl azide onto an aldehyde would generate a diazonium cation intermediate (Scheme 2,  $\text{R}^1 = \text{H}$ ). Then elimination of proton with the synchronous loss of nitrogen gas would afford an amide as the product. The cleavage of C–Si bond might be easier than that of C–H bond under the acidic conditions. Therefore, if a silyl group was attached to the carbonyl unit, then the intermolecular Schmidt reaction could be more efficient (Scheme 2,  $\text{R}^1 = \text{silyl group}$ ). For this envision to be successful, the following three key points should be concerned: (1) could the azide attack proceed effectively when the electronic effect and steric effect of the carbonyl group were obviously changed by introducing a silyl group? (2) Would the decomposition of the acyl silane to an aldehyde occur before the Schmidt reaction? (3) Could the migration of the R group or a silyl group ( $\text{R}^1 = \text{Si}$ ) to the nitrogen atom take place when the acyl silane was employed?

With the above considerations, the acyl silane **1a** and *n*-heptyl azide **2a** were selected as the model substrates for this investigation. A series of Lewis acids and Brønsted acids were examined

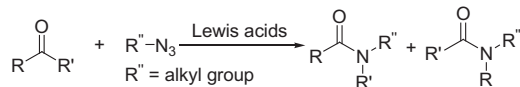
\* Corresponding author. Tel.: +86 (951)206 2274; fax: +86 (951)206 2323.

E-mail address: [rui.li@nxu.edu.cn](mailto:rui.li@nxu.edu.cn) (R. Li).

Boyer's work:

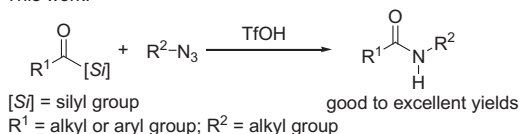


Aubé's work:

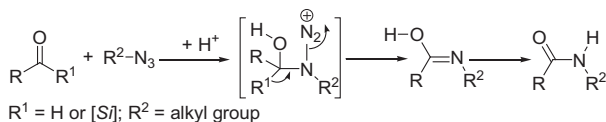


Aldehyde:  $\text{R}' = \text{H}$ , Low to moderate yields and regioselectivities  
 Ketone:  $\text{R}' = \text{alkyl group}$ , only good result for limited substrates

This work:

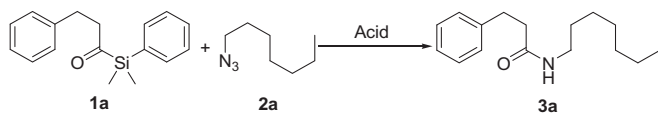


**Scheme 1.** Intermolecular Schmidt reaction of alkyl azides with carbonyl compounds.



**Scheme 2.** Proposed intermolecular Schmidt reaction of alkyl azides with acyl silanes.

**Table 1**  
 Optimization of the intermolecular Schmidt reaction of alkyl azide **2a** with acyl silane **1a**<sup>a</sup>



Entry	Acid	Ratio of <b>1a/2a</b>	Time	Yield <sup>b</sup> (%)
<b>1<sup>c</sup></b>	<b>BF<sub>3</sub>·OEt<sub>2</sub></b>	1:1.8	40 h	76
<b>2</b>	<b>TfOH</b>	<b>1:1.8</b>	<b>10 min</b>	<b>95</b>
<b>3<sup>d</sup></b>	Et <sub>2</sub> AlCl	1:1.8	20 h	0
4	SnCl <sub>4</sub>	1:1.8	15 min	53
5	TiCl <sub>4</sub>	1:1.8	15 min	71
6	TFA	1:1.8	65 h	—
7	TfOH	1:2.5	10 min	95
8	TfOH	1:1.5	10 min	80
9	TfOH	1:1.2	10 min	67
10	TfOH (1.2 equiv)	1:1.8	48 h	86
11	TfOH (1.2 equiv)	1:2.5	24 h	94
12	TfOH (3.0 equiv)	1:1.2	10 min	90

<sup>a</sup> Reaction of acyl silane **1a** (134.2 mg, 0.50 mmol) and alkyl azide **2a** with the acid promoter (1.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at room temperature.

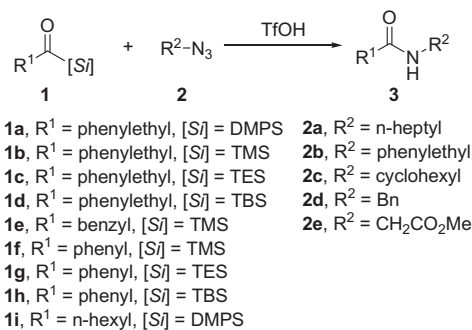
<sup>b</sup> Isolated yield after purification.

<sup>c</sup> Reaction at 0 °C.

<sup>d</sup> Reduction of **1a** to an  $\alpha$ -hydroxysilane.

for the reaction, and the ratio of **2a** to **1a** was 1.8 to 1. It was very exciting that the intermolecular Schmidt reaction could be realized by most of the promoters, where all the reactions were carried out with 2.0 equiv of promoters. The reaction of azide **2a** and acyl silane **1a** was absolutely site selective, and the competitive migration of alkyl group or dimethylphenylsilyl group (DMPS) to nitrogen atom was not observed. Among them, the TfOH-promoted reaction gave amide **3a** in 95% yield (Table 1, entry 2), and the conversion was completed in 10 min. Further evaluation revealed that

**Table 2**  
 Scope of substrates<sup>a</sup>



Entry	Acyl silane <b>1</b>	Alkyl azide <b>2</b>	<b>3</b>	Yield <sup>b</sup> (%)
1	<b>1a</b>	<b>2a</b>	<b>3a</b>	95
2	<b>1a</b>	<b>2b</b>	<b>3b</b>	93
3	<b>1a</b>	<b>2c</b>	<b>3c</b>	83
4	<b>1a</b>	<b>2d</b>	<b>3d</b>	75
5	<b>1a</b>	<b>2e</b>	<b>3e</b>	89
6	<b>1b</b>	<b>2a</b>	<b>3a</b>	96
7	<b>1b</b>	<b>2c</b>	<b>3c</b>	88
8	<b>1b</b>	<b>2e</b>	<b>3e</b>	93
9	<b>1c</b>	<b>2a</b>	<b>3a</b>	89
10	<b>1c</b>	<b>2e</b>	<b>3e</b>	89
11	<b>1d</b>	<b>2a</b>	<b>3a</b>	95
12	<b>1d</b>	<b>2b</b>	<b>3b</b>	97
13	<b>1e</b>	<b>2a</b>	<b>3f</b>	98
14	<b>1e</b>	<b>2b</b>	<b>3g</b>	92
15	<b>1e</b>	<b>2d</b>	<b>3h</b>	81
16	<b>1f</b>	<b>2a</b>	<b>3i</b>	96
17	<b>1f</b>	<b>2b</b>	<b>3j</b>	99
18	<b>1g</b>	<b>2a</b>	<b>3i</b>	88
19	<b>1g</b>	<b>2e</b>	<b>3k</b>	74
20	<b>1g</b>	<b>2e</b>	<b>3k</b>	89 <sup>c</sup>
21	<b>1h</b>	<b>2a</b>	<b>3i</b>	90
22	<b>1h</b>	<b>2b</b>	<b>3j</b>	77
23	<b>1h</b>	<b>2b</b>	<b>3j</b>	87 <sup>c</sup>
24	<b>1i</b>	<b>2a</b>	<b>3l</b>	87
25	<b>1i</b>	<b>2b</b>	<b>3m</b>	91

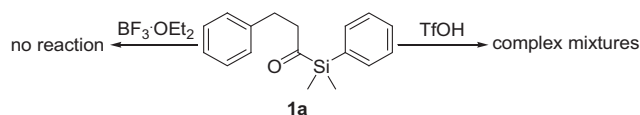
<sup>a</sup> Reaction of acyl silane **1** (0.50 mmol) and alkyl azide **2** (0.90 mmol) with TfOH (150.0 mg, 1.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at room temperature for 10–30 min.

<sup>b</sup> Isolated yield after purification.

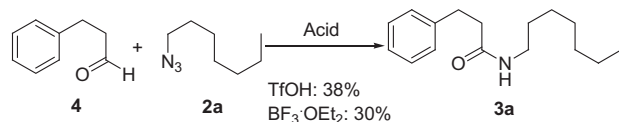
<sup>c</sup> Reaction of acyl silane **1** (0.50 mmol) and alkyl azide **2** (0.60 mmol) with TfOH (225.0 mg, 1.50 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at room temperature for 10 min.

the yield for **3a** could not be improved by increasing the dosage of *n*-heptyl azide (Table 1, entry 7). If the reaction was promoted by 1.2 equiv of TfOH, then the amide **3a** could be obtained in 86% yield with significantly prolonged reaction time (Table 1, entry 10). When more TfOH (3.0 equiv) was employed, the amount of **2a** could be obviously reduced, and the amide **3a** was delivered in 90% yield (Table 1, entry 12).

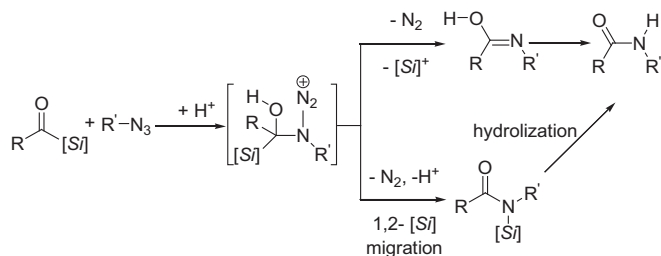
After integrated consideration, the optimal reaction conditions (in bold, Table 1, entry 2) were selected for substrate investigation. First, the scope of azides was examined (Table 2, entries 1–5). Just like the *n*-heptyl azide **2a**, four other alkyl azides including phenylethyl azide **2b**, cyclohexyl azide **2c**, benzyl azide **2d**, and methyl azidoacetate **2e** all reacted well with the acyl silane **1a**, affording the corresponding amides **3b–3e** with good to excellent yields. Among them, the benzyl azide **2d** exhibited slightly lower reactivity, which might be due to the competitive decomposition of **2d** to an iminium salt under the acidic conditions.<sup>6b,11</sup> Further experiments indicated that several different silyl groups, such as TMS, TES, and TBS, all matched this conversion well (Table 2, entries 6–12). Excellent results were also observed with the reaction of phenylacetyl silane **1e** (Table 2, entries 13–15). Similarly, when the benzyl azide **2d** was used, amide **3h** was



**Scheme 3.** The acid resistance experiments of acyl silane **1a**.



**Scheme 4.** Intermolecular Schmidt reaction of hydrocinnamic aldehyde **4** with *n*-heptyl azide **2a**.



**Scheme 5.** Possible mechanism for the Schmidt reaction of alkyl azides with acyl silanes.

obtained with only 81% yield. Then the benzoyl silanes **1f**, **1g** and **1h** were explored, generally affording the amides **3i–3j** with compatible yields (Table 2, entries 16–23). The conversion seemed to be less efficient with some cases (Table 2, entries 19 and 22). Fortunately, the yields were substantially improved when the reaction conditions for entry 12 in Table 1 were used (Table 2, entries 20 and 23). Finally, the *n*-hexylacyl silane **1i** was explored with azides **2a** and **2b**, and the yields for amides **3i** and **3m** were 87% and 91%, respectively.

It should be noted that the Schmidt reaction of alkyl azides with the corresponding aldehydes could also produce amides **3**. Several more experiments were performed to illustrate the possible process for the reaction of acyl silanes and alkyl azides. First, the acid resistance experiments of **1a** was examined with TfOH and  $\text{BF}_3 \cdot \text{OEt}_2$  (Scheme 3). Absolute decomposition of **1a** was observed with TfOH (2.0 equiv) at room temperature, affording very complicated mixtures. From NMR of the crude, it indicated that the silyl group of **1a** was removed, however no hydrocinnamic aldehyde **4** was generated. Further, the silane **1a** was stable with  $\text{BF}_3 \cdot \text{OEt}_2$  (2.0 equiv) at 0 °C for 48 h. The intermolecular Schmidt reactions of *n*-heptyl azide **2a** with aldehyde **4** were also treated with TfOH and  $\text{BF}_3 \cdot \text{OEt}_2$ , and both reactions produced amide **3a** in poor yields (Scheme 4).

The above experimental results could basically rule out the possibility of the conversion proceeding through the desilylation of acyl silanes followed by a Schmidt process. The silyl group attached to the carbonyl unit might accelerate the intermolecular

Schmidt reaction. The proposed mechanism (Scheme 2) involving the azide attack to acyl silane followed by elimination of the silyl group and nitrogen gas might be reasonable. Further, another process via 1,2-migration of the silyl group to nitrogen atom could also be possible (Scheme 5), where the silyl group would be removed under the acidic conditions.

In summary, we have designed and realized an efficient intermolecular Schmidt reaction of alkyl azides with acyl silanes. The electrophiles for the Schmidt reaction were successfully expanded to the acyl silanes, and absolute site selectivity was observed with the rearrangement. The conversion was efficient with a wide range of substrates, and amides were obtained in good to excellent yields. Further evaluation of other carbonyl compounds for the Schmidt reaction is underway in our laboratory.

## Acknowledgment

This work was supported by the Ningxia Natural Science Foundation (NZ15035).

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2016.06.124>.

## References and notes

- For two recently selected reviews, see: (a) Wroblewski, 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*; Bräse, S., Banert, K., Eds.; Wiley: Weinheim, 2010; pp 191–237.
- Gorin, D. J.; Davis, N. R.; Toste, D. F. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261.
- (a) 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; (b) Li, X.-J.; Qiao, J.-B.; Sun, J.; Li, X.-Q.; Gu, P. *Org. Lett.* **2014**, *16*, 2865–2867; (c) Wang, B.-J.; Xue, P.; Gu, P. *Chem. Commun.* **2015**, 2277–2279; (d) Li, Q.; Li, R.; Li, X.; Gu, P. *Chin. J. Org. Chem.* **2015**, *35*, 2326–2332.
- (a) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–954; (b) Boyer, J. H.; Morgan, L. R., Jr. *J. Org. Chem.* **1959**, *24*, 561–562.
- Lee, H.-L.; Aubé, J. *Tetrahedron* **2007**, *63*, 9007–9015.
- (a) Aubé, J.; Milligan, G. L.; Mossman, C. J. *J. Org. Chem.* **1992**, *57*, 1635–1637; (b) Desai, P.; Schildknecht, K.; Agrios, K.; Mossman, A. C. J.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232; (c) Gracias, V.; Frank, K. E.; Milligan, G. L.; Aubé, J. *Tetrahedron* **1997**, *53*, 16241–16252.
- For Schmidt reaction of azido alkanols with aldehydes: (a) Badiang, J. G.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 2484–2487; (b) Boyer, J. H.; Canter, F. C.; Hamer, J.; Putney, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 325–327; (c) Boyer, J. H.; Hamer, J. *J. Am. Chem. Soc.* **1955**, *77*, 951–954; For Schmidt reaction of azido alkanols with ketones: (d) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Am. Chem. Soc.* **1995**, *117*, 8047–8048; (e) Gracias, V.; Milligan, G. L.; Aubé, J. *J. Org. Chem.* **1996**, *61*, 10–11; (f) Forsee, J. E.; Aubé, J. *J. Org. Chem.* **1999**, *64*, 4381–4385; (g) Forsee, J. E.; Aubé, J. *Org. Lett.* **1999**, *1*, 495–498; (h) Smith, B. T.; Gracias, V.; Aubé, J. *J. Org. Chem.* **2000**, *65*, 3771–3774; (i) Katz, C. E.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 13948–13949; (j) Sahasrabudhe, K.; Gracias, V.; Fumess, K.; Sminth, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922.
- Gu, P.; Sun, J.; Kang, X.-Y.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. *Org. Lett.* **2013**, *15*, 1124–1127.
- (a) Kulkarni, S. S.; Hu, X.; Manetsch, R. *Chem. Commun.* **2013**, 1193–1195; (b) Carbone, G.; Burnley, J.; Moses, J. E. *Chem. Commun.* **2013**, 2759–2761; (c) Xie, S.; Ramström, O.; Yan, M. *Org. Lett.* **2015**, *17*, 636–639; (d) Xie, S.; Zhang, Y.; Ramström, O.; Yan, M. *Chem. Sci.* **2016**, *7*, 713–718.
- (a) Zhou, B.; Yang, Y.; Shi, J.; Feng, H.; Li, Y. *Chem.-Eur. J.* **2013**, *19*, 10511–10515; (b) Jin, L. M.; Lu, H.; Cui, Y.; Lizardi, C. L.; Arzuza, T. N.; Wojtas, L.; Cui, X.; Zhang, X. P. *Chem. Sci.* **2014**, *5*, 2422–2427.
- Wroblewski, A.; Aubé, J. *J. Org. Chem.* **2001**, *66*, 886–889.