

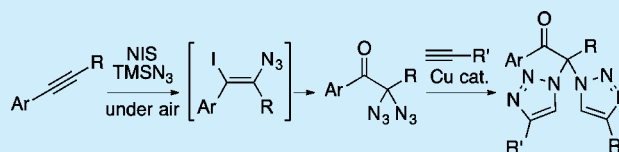
# Regioselective Iodoazidation of Alkynes: Synthesis of $\alpha,\alpha$ -Diazidoketones

Noriko Okamoto, Takuya Sueda, Hideki Minami, Yoshihisa Miwa, and Reiko Yanada\*

Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan

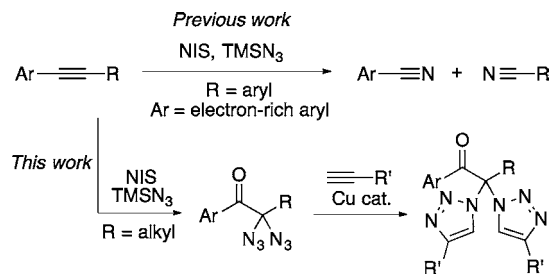
**S** Supporting Information

**ABSTRACT:** Aryl alkyl alkynes reacted with *N*-iodosuccinimide (NIS) and trimethylsilyl azide (TMSN<sub>3</sub>), leading to  $\alpha,\alpha$ -diazidoketones via the regioselective addition of IN<sub>3</sub> to alkynes. Huisgen cyclization of  $\alpha,\alpha$ -diazidoketones generated bis-triazole compounds.



Alkynes have the potential to be transformed into various functional groups and are considered as one of the most important compounds.<sup>1–3</sup> We explored the development of novel tandem reactions utilizing alkyne reactivity.<sup>4</sup> We recently reported the cleavage of an alkyne triple bond into two nitriles in the absence of a metal catalyst (Scheme 1).<sup>4b</sup> Triple bond

**Scheme 1. Synthesis of  $\alpha,\alpha$ -Diazidoketone and Huisgen Cyclization**



cleavage of *diarylalkynes* tends to proceed in the presence of at least one electron-donating group (EDG) on the benzene ring. The reaction of *aryl alkyl substituted alkynes* is somewhat complicated, generating nitriles in low yield. Thus, we investigated the reactivity of other alkynes and found that a novel reaction of *aryl alkyl substituted alkynes* with *N*-iodosuccinimide (NIS) and trimethylsilyl azide (TMSN<sub>3</sub>) yielded  $\alpha,\alpha$ -diazidoketones regioselectively. The cleavage of an alkyne triple bond or the formation of  $\alpha,\alpha$ -diazidoketone depends on the electron-donating ability of substituents on the aromatic ring. This transformation represents the formal addition of two heteroatoms on each alkyne sp carbon, which represents the first synthesis of  $\alpha,\alpha$ -diazidoketones from alkynes. Several methods to access  $\alpha,\alpha$ -diazido carbonyl compounds with NaN<sub>3</sub> and other reagents have been reported.<sup>5</sup> Herein, we describe highly regioselective iodoazidation of alkynes to  $\alpha,\alpha$ -diazidoketones<sup>6</sup> by NIS and TMSN<sub>3</sub>. These diazidoketones are relatively stable and could be subjected to Huisgen cyclization<sup>2,7</sup> (Scheme 1).

The reaction of alkyne **1** with TMSN<sub>3</sub> and NIS was performed under a nitrogen atmosphere at room temperature

to afford  $\alpha,\alpha$ -diazidoketone **3**<sup>8</sup> via alkene **2**,<sup>9</sup> which was assumed to be an intermediate (Table 1). Alkene **2** was

**Table 1. Optimization of Reaction Conditions<sup>a</sup>**

| entry           | NIS (equiv) | TMSN <sub>3</sub> (equiv) | conditions            | time (day) | 2 (%) | 3 (%) |
|-----------------|-------------|---------------------------|-----------------------|------------|-------|-------|
| 1               | 2.2         | 2.2                       | under N <sub>2</sub>  | 2          | 4     | 42    |
| 2               | 1.1         | 1.1                       | under N <sub>2</sub>  | 2          | 66    | 9     |
| 3               | 1.1         | 2.2                       | under N <sub>2</sub>  | 2          | 60    | 13    |
| 4               | 2.2         | 1.1                       | under N <sub>2</sub>  | 2          | 63    | 15    |
| 5               | 3           | 3                         | under N <sub>2</sub>  | 2          | trace | <35   |
| 6 <sup>b</sup>  | 2.2         | 2.2                       | under N <sub>2</sub>  | 1          | 7     | 38    |
| 7 <sup>c</sup>  | 2.2         | 2.2                       | under N <sub>2</sub>  | 1          | 19    | <26   |
| 8               | 2.2         | 2.2                       | under N <sub>2</sub>  | 0.4        | trace | 69    |
| 9               | 1.1         | 2.2                       | under N <sub>2</sub>  | 0.4        | trace | 65    |
| 10              | 0.5         | 2.2                       | under N <sub>2</sub>  | 8          | 35    | 12    |
| 11 <sup>d</sup> | 1.1         | 2.2                       | under N <sub>2</sub>  | 0.4        | trace | 70    |
| 12              | 1.1         | 2.2                       | in the dark under air | 0.4        | trace | 66    |

<sup>a</sup>Alkyne **1** (0.6 mmol) in MeCN/DCE (1.5 mL/1.5 mL) was used. <sup>b</sup>50 °C. <sup>c</sup>0.56 equiv of H<sub>2</sub>O was added. <sup>d</sup>0.1 M.

unstable in solution under irradiation with visible light. The stereochemistry of the C–C double bond of **2** was *Z* geometry based on X-ray crystallography.<sup>10</sup> As the reaction proceeded, the color of the reaction mixture changed from yellow-orange<sup>11</sup> of iodine azide (IN<sub>3</sub>) to dark purple of iodine. For the formation of **3**, 2.2 equiv of each reagent were required (entries 1–4). Attempts to improve the yield of **3** (by increasing the amount of each reagent, changing the reaction temperature, and adding water) were not successful (entries 5–7). While examining the reaction conditions, we found that the reaction was faster and cleaner under air than under nitrogen (entry 8).

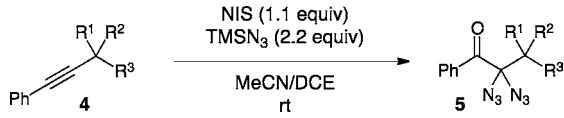
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Even 1.1 equiv of NIS was sufficient to complete the reaction, but a catalytic amount of NIS was insufficient (entry 9 vs 10). The yield of **3** was highest when the concentration of **1** was decreased to 0.1 M (entry 11). The reaction in a dark room under air also proceeded smoothly to afford **3** (entry 9 vs 12). This may imply that  $\alpha,\alpha$ -diazidoketone **3** is not formed by a radical process.<sup>12</sup> The above-described results can be summarized as follows: (1) Oxygen in air is required for  $\alpha,\alpha$ -diazidoketone formation and is thought to oxidize iodide ions to iodine (entry 3 vs 9), (2) water added to the reaction mixture interferes with the reaction because of the facile hydrolysis of TMSN<sub>3</sub> (entry 1 vs 7), (3) moisture in air is needed for the formation of **3**, and (4) the source of carbonyl oxygen and the reaction mechanism remain unclear.

Using these optimized conditions, the substrate scope was explored (Table 2). Regarding the protecting group of alcohol,

Table 2. Scope of Alkyne **4**<sup>a</sup>



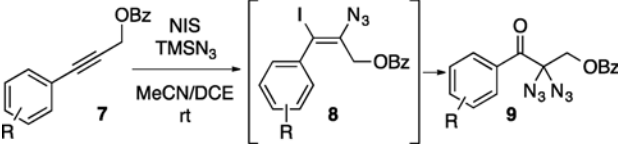
| entry | <b>4</b>  | R <sup>1</sup>   | R <sup>2</sup> | R <sup>3</sup> | time (day) | <b>5</b> (%)               |
|-------|-----------|--|----------------|----------------|------------|----------------------------|
| 1     | <b>4a</b> | OAc  | H              | H              | 1.2        | <b>5a</b> , 68             |
| 2     | <b>4b</b> | OCO <sub>2</sub> Et  | H              | H              | 1.2        | <b>5b</b> , 72             |
| 3     | <b>4c</b> | OCOC <sub>6</sub> H <sub>4</sub> p-Br  | H              | H              | 2          | <b>5c</b> , 73             |
| 4     | <b>4d</b> | OBn  | H              | H              | 7          | <b>5d</b> , 17             |
| 5     | <b>4e</b> | OTBS   | H              | H              | 7          | <b>5e</b> , 35             |
| 6     | <b>4f</b> | CH <sub>2</sub> CH <sub>2</sub> OBz  | H              | H              | 0.4        | <b>5f</b> , 62             |
| 7     | <b>4g</b> | CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OBz                                | H              | H              | 0.4        | <b>5g</b> , 58             |
| 8     | <b>4h</b> | Pr   | H              | H              | 0.4        | <b>5h</b> , 62             |
| 9     | <b>4i</b> | -CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> - | H              | H              | 3          | <b>5i</b> , 36             |
| 10    | <b>4j</b> | OBz  | Me             | H              | 1          | <b>5j</b> , 70             |
| 11    | <b>4k</b> | OBz  | Ph             | H              | 1          | <b>5k</b> , 58             |
| 12    | <b>4l</b> | OBz  | Me             | Me             | 7          | <b>5l</b> , 0 <sup>b</sup> |

<sup>a</sup>Alkynes **4** (0.3 mmol) in MeCN/DCE (1.5 mL/1.5 mL) were used. <sup>b</sup>2-Iodo-3-methyl-1-phenylbut-2-en-1-one **6** was obtained in 73% yield.

the reaction was tolerant to acyl-type protecting groups (entries 1–3). The structure of  $\alpha,\alpha$ -diazidoketone was determined using X-ray crystallographic analysis of **5c**.<sup>13</sup> Ether-type protecting groups were not suitable (entries 4 and 5). Internal alkynes excluding propargyl alcohol derivatives could also be used (entries 6–8), but cyclohexyl-substituted **4i** afforded **5i** in low yield (entry 9). Secondary propargyl alcohol derivatives also yielded **5j** and **5k** (entries 10 and 11). Tertiary propargyl alcohol derivative **4l** underwent elimination of benzoate to afford  $\alpha$ -iodo- $\alpha,\beta$ -unsaturated ketone **6** (entry 12).

We next examined the effect of an aromatic substituent (Table 3). Alkynes that have substituents (excluding a strong EDG and EWG (electron-withdrawing group)) on the aromatic ring could afford diazidoketones **9** (entries 2–4 and 6). The use of methoxy-substituted **7a** resulted in elimination, similar to **4l** (entry 1). Nitro-substituted **7e** showed low reactivity and yielded a complex mixture, probably due to a decrease in the electron density of the alkyne triple bond (entry 5). We found that *ortho*-substituted aryl alkynes **7g**–**7j** did not afford diazidoketones; alkenes **8g**–**8j** were the major products (entries 7–10). The structure of **8g** was also determined using X-ray crystallography.<sup>14</sup> <sup>1</sup>H NMR spectra of **8g**–**8j**

Table 3. Scope of Alkyne **7**<sup>a</sup>



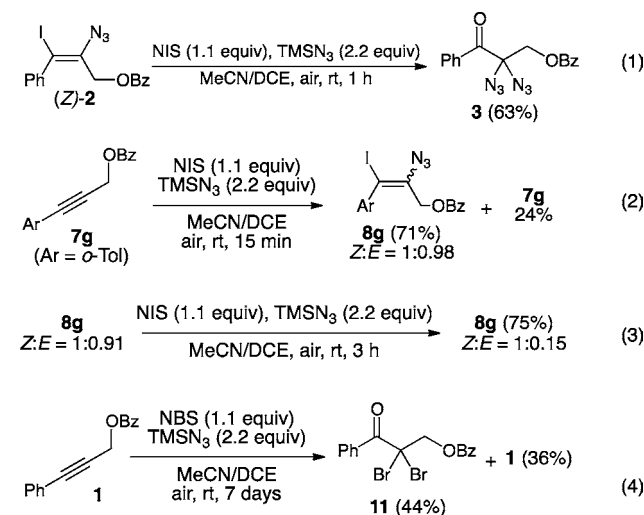
| entry | <b>7</b>  | R  | time (day) | <b>8</b> (%)                 | <b>9</b> (%)   |
|-------|-----------|--|------------|------------------------------|----------------|
| 1     | <b>7a</b> | 4-MeO  | 1.2        | 0 <sup>b</sup>               |                |
| 2     | <b>7b</b> | 4-Me   | 1.2        | trace                        | <b>9b</b> , 72 |
| 3     | <b>7c</b> | 4-F  | 2          | trace                        | <b>9c</b> , 66 |
| 4     | <b>7d</b> | 4-CF <sub>3</sub>                            | 7          | trace                        | <b>9d</b> , 50 |
| 5     | <b>7e</b> | 4-NO <sub>2</sub>                            | 7          | 0 <sup>c</sup>               |                |
| 6     | <b>7f</b> | 3-MeO  | 0.4        | trace                        | <b>9f</b> , 65 |
| 7     | <b>7g</b> | 2-Me   | 0.4        | ( <i>Z</i> )- <b>8g</b> , 81 | 0              |
| 8     | <b>7h</b> | 2- <i>i</i> -Pr                              | 0.4        | <b>8h</b> , 77               | 0              |
| 9     | <b>7i</b> | 2-Ph   |            | <b>8i</b> , 80               | 0              |
| 10    | <b>7j</b> | R-C <sub>6</sub> H <sub>4</sub> = 1-naphthyl | 1          | <b>8j</b> , 79               | 0              |

<sup>a</sup>Alkynes **7** (0.3 mmol) in MeCN/DCE (1.5 mL/1.5 mL) was used. <sup>b</sup>2-Iodo-1-(4-methoxyphenyl)prop-2-en-1-one **10** was obtained in 51% yield. <sup>c</sup>Complex mixture.

exhibited an AB system for allylic protons, suggesting the existence of atropisomerism.<sup>15</sup>

We performed the following experiments with the aim of obtaining an understanding of the reaction mechanism. When isolated (*Z*)-**2** was treated with NIS and TMSN<sub>3</sub> under air, diazidoketone **3** was formed in a similar yield, indicating that **2** was an intermediate in the diazidoketone formation (Scheme 2,

Scheme 2. Mechanistic Studies

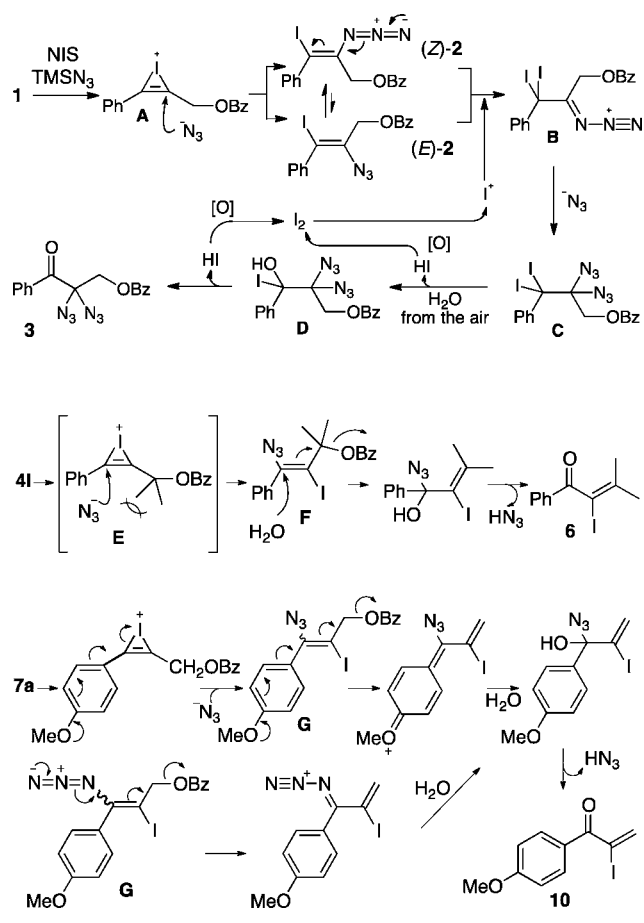


eq 1). When the reaction of **7g** was quenched after 15 min, an inseparable 1:1 mixture of (*Z*)- and (*E*)-**8g** was obtained (eq 2). Treatment of this mixture for a further 3 h with NIS and TMSN<sub>3</sub> yielded (*Z*)-**8g** as a major product (eq 3). These results suggest isomerization of the C–C double bond of **8g**, although the reasons are not yet clear. Computational studies indicated that (*E*)-**8g** was 2.2 kcal/mol higher in energy than (*Z*)-**8g**.<sup>16</sup> A similar trend was observed, and (*E*)-**2** was calculated to be 1.8 kcal/mol higher than the (*Z*)-isomer. The higher stability of the *Z*-alkenes may be a manifestation of the “cis-effect”.<sup>17</sup> The use of NBS instead of NIS afforded  $\alpha,\alpha$ -dibromoketone **11** as the result of a normal ionic addition<sup>18–21</sup>

but did not complete the reaction to recover the starting material (eq 4).

A plausible reaction mechanism for the formation of  $\alpha,\alpha$ -diazidoketone is shown in Scheme 3. Initially, alkyne **1** reacts

Scheme 3. Plausible Reaction Mechanism



with NIS and  $\text{TMSN}_3$  to form regiochemically unusual alkene (Z)-**2** or (E)-**2** via *syn* or *anti* addition of the azide ion to intermediate **A**. Hassner et al. reported that the regioselectivity of the addition of  $\text{IN}_3$  to aryl alkyl alkyne is opposite to the predicted regioselectivity based on the electronic effect and that  $\text{IN}_3$  addition results in the formation of two stereoisomers.<sup>22</sup> We performed the reaction of alkyne **1** with  $\text{IN}_3$  produced by Hassner's method.<sup>11</sup> The  $^1\text{H}$  NMR time courses for the conversion of alkyne **1** into alkenes **2** and diazidoketone **3** were similar, indicating that the active species from the reaction of NIS and  $\text{TMSN}_3$  is ionic  $\text{IN}_3$ . The reaction of **B** with an azide ion affords **C**. Thus, **C** is subjected to the following through hydrolysis by moisture from the air and elimination of HI to generate diazidoketone **3** by way of intermediate **D**. Oxygen oxidizes HI to iodine, which acts as the  $\text{I}^+$  source to add to the remaining **2**. *Ortho*-substituents of **8g**–**8j** likely complicated the second  $\text{IN}_3$  addition. When NBS was used, the addition of  $\text{BrN}_3$  may proceed in the normal regiochemical manner, forming alkenes with a higher reactivity toward  $\text{BrN}_3$  than the starting alkyne. For these reasons, double addition of  $\text{BrN}_3$  to alkyne followed by hydrolysis at the benzylic position afforded  $\alpha,\alpha$ -dibromoketone **11**. For alkyne **4l**, alkene **F** is formed because of the steric hindrance of **E**.<sup>11</sup> Formation of **6** appears to be due to  $\text{S}_{\text{N}}2'$  attack of  $\text{H}_2\text{O}$  in alkene **F**. On the other hand,

the reaction of **7a** is strongly influenced by the effect of the methoxy group, and regioselective addition of  $\text{IN}_3$  exclusively affords alkene **G**. The key difference between alkene **G** and substrates in our previous report<sup>4b</sup> is the existence of the leaving group: a benzoyloxy group. Because of the two EDGs (methoxyphenyl and azido groups), the benzoyloxy group is easily eliminated to afford **10**.

Finally,  $\alpha,\alpha$ -diazidoketone **5a** underwent Huisgen cyclization (Table 4). Two azido groups of  $\alpha,\alpha$ -diazidoketone reacted with

Table 4. Huisgen Cyclization of  $\alpha,\alpha$ -Diazidoketone

| entry | R'                                | time (h) | <b>12</b> (%)   |
|-------|-----------------------------------|----------|-----------------|
| 1     | <i>n</i> -Bu                      | 2        | <b>12a</b> , 87 |
| 2     | <i>i</i> -Pr                      | 3        | <b>12b</b> , 82 |
| 3     | cyclopropyl                       | 3        | <b>12c</b> , 89 |
| 4     | <i>t</i> -Bu                      | 24       | <b>12d</b> , 57 |
| 5     | TMS                               | 24       | trace           |
| 6     | 4-MeC <sub>6</sub> H <sub>4</sub> | 7        | <b>12e</b> , 85 |

the terminal alkyne, providing bis-triazole compound **12**. Both alkyl- and aryl-substituted alkynes can be used. However, the use of trimethylsilylacetylene resulted in decreased reactivity and recovery of some of the substrate (entry 5). The reaction of **5a** with 1 equiv of alkyne resulted in the low yield of **12** and recovery of **5a**, not affording the monotriazole compound.

In conclusion, we described a novel transformation of aryl alkyl alkynes not having strong EDG and EWG substituents on the aromatic ring to  $\alpha,\alpha$ -diazidoketones using NIS and  $\text{TMSN}_3$ . Although the mechanism of this reaction is still unclear, the reaction probably proceeds via the addition of  $\text{IN}_3$  to an alkyne. Huisgen cyclization of  $\alpha,\alpha$ -diazidoketones afforded bis-triazoles in good yield.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details, spectral data for all new compounds, and X-ray data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: [ryanada@ps.hirokoku-u.ac.jp](mailto:ryanada@ps.hirokoku-u.ac.jp)

### Notes

The authors declare no competing financial interest.

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