Transformations of 1-(Oxiranylmethyl)-1,2,3-triazoles into 2-(Oxiranylmethyl)-1,2,3-triazoles and Alkenenitrides

Ayumi Osawa, Akane Mera, Kosuke Namba,* and Keiji Tanino*

Department of Chemistry, Graduate School of Science, Hokkaido University, Kita-ku, Sapporo 060-0810, Japan
FAX: (+81) 11-706-4920; E-mail:namba@mail.sci.hokudai.ac.jp and ktanino@sci.hokudai.ac.jp

Abstract: New reactions for transformation of 1-(oxiranylmethyl)-1,2,3-triazoles into 2-(oxiranylmethyl)-1,2,3-triazoles or alkenenitrides were established. Successive treatment of the substrate with triflic acid and t-BuOH afforded 4,6-dihydro-5-hydroxy-1,3a,6a-triazapentalene derivative. Under the influence of NaH, the bicyclic compound was converted to a 2-(oxiranylmethyl)-1,2,3-triazole or an alkenenitrile. The reaction pathway depends on the substituent pattern of the epoxide side chain.

Key words: 1,2,3-triazole, 2-substituted-1,2,3-triazole, click reaction.

The Cu-mediated Huisgen cycloaddition reaction developed by Sharpless and co-workers has received a great deal of attention as one of the most powerful click reaction applicable to the area of material science, drug discovery, polymer chemistry, bioconjugation, and so on.\textsuperscript{1,2} The reaction consists of Cu(I)-catalyzed azide/alkyne condensation to regioselectively provide 1-substituted-1H-1,2,3-triazoles under mild conditions, and a large number of 1-substituted-1H-1,2,3-triazole derivatives have been reported as useful compounds.\textsuperscript{3} In contrast, much less attention has been paid to 2-substituted-2H-1,2,3-triazoles due to its difficulty of preparation. Therefore, development of efficient synthetic method for the 2-substituted-1,2,3-triazoles has recently been an active research area.\textsuperscript{4} Meanwhile, inspired by the click reaction, we have recently established the direct synthesis of 1,3a,6a-triazapentalene, an excellent fluorescent chromophore with a compact structure, from an alkyn and azide.\textsuperscript{5} The click reaction of azide I possessing two triflates at each of the C2 and C3 positions afforded a triazole A, which underwent cyclization to give a triazolium ion B. In the presence of triethylamine, the intermediate B was subsequently converted to triazapentalene 3 by a sequential reaction of E2 elimination and deprotonation (Scheme 1a). Furthermore, 5-methoxy analog of B was found to be stable enough for isolation, and strong base was necessary for elimination of methoxy group to give 1,3a,6a-triazapentalenes.\textsuperscript{6} Based on these synthetic studies of 1,3a,6a-triazapentalenes, we newly planned the direct synthesis of 2-substituted-2H-1,2,3-triazoles, that is, the use of oxiranylmethyl azides 4 as an azide fragment (Scheme 1b). The Cu-mediated click reaction of 4 with an alkyn would give 1-(oxiranylmethyl)-1,2,3-triazole 5 which may undergo a cyclization reaction to afford bicyclic triazolium ion B’. The formation of alkoxide ion at B’ would not induce the elimination to afford 1,3a,6a-triazapentalenes and reform the epoxide ring at C4 position to give 2-oxiranylmethyl-1,2,3-triazole 6 as depicted in scheme 1b. However, the alternative epoxide ring-closing mode at C6 position is also possible, which convert back to the 1-oxiranylmethyl-1,2,3-triazole 5. Therefore, the control of regioselectivity in epoxide ring-closing reaction is an important issue of this conversion strategy for giving 2-substituted-1,2,3-triazoles (Scheme 1b).

Scheme 1. Synthetic approach to the 1,3,6a-triazapentalenes possessing various substituents.

We undertook the investigation with the simplest oxiranylmethyl azide 4 in order to elucidate the regioselectivity of epoxide reforming reaction. The click reaction of oxiranylmethyl azide 4, generated from epichlorohydrin (7) in situ, with 1-pentadecyne afforded the triazole 5a in 81% yield.\textsuperscript{7} Since the cascade cyclization of 5a after triazole formation was not occurred, the activation of epoxide ring was examined. Initial attempts to activate the epoxide moiety of 5a by using a catalytic amount of Brønsted
or Lewis acids were fruitless due to the basicity of the triazole ring. On the other hand, treatment of 5a with 2.0 equiv of trifluoromethanesulfonic acid (TfOH) in dichloromethane unexpectedly afforded triflate 8a through a regioselective epoxide opening reaction.10 Since oxiranes are known to easily undergo ring-opening polymerization in the presence of a strong acid, formation of triflate 8a may come from the positive charge on the protonated triazole ring which prevents the dimerization or origomerization of 5a.10 Although the protonated triazole ring of 8a did not attack the triflate moiety in situ, formation of the desired bicyclic triazolium ion 9a in 87% NMR yield was observed after extraction of 8a with water. In contrast, one-pot neutralization of the reaction mixture by adding a base merely induced reformation of the starting material 5a. These results led us to explore neutral proton acceptors other than water, and addition of an excess amount of t-BuOH was found to effect the desired transformation (Scheme 2). Having established the procedure for preparing 5-hydroxy-intermediate 9a, direct transformation into 2-oxiranlymethyl-1,2,3-triazole 6a under basic conditions was examined. After removal of dichloromethane and t-BuOH under reduced pressure, the crude 9a was diluted with THF, and to this was carefully added 3.5 equiv of sodium hydride. The reaction proceeded smoothly at room temperature, but we were surprised to find that the product was nitrile 10 (70% yield from 5a) (Scheme 2). Meanwhile, direct treatment of 5a with sodium hydride never gave nitrile 10.11

Although the mechanistic details of the surprising reaction is not clear, we investigated the substituent effect of the epoxide side chain (Table 1). The direct sequential treatment of methyl substituted analog 5b with TfOH, t-BuOH, and NaH also afforded the same nitrile 10 in 51% yield (entry 1). The reaction of the corresponding diastereomer 5c also gave 10 in 73% yield, indicating that the stereochemistry at the side chain of the triazole do not affect the nitrile formation reactions. The phenyl substituent instead of a methyl group also afforded the same nitrile 10 in 60% yield (entry 3). Since the hydrogen atom at C4 position was considered to be important factor affecting nitrile forming reaction, gem-dimethyl substituted analog 5e was examined. Interestingly, the desired epoxide formation occurred to predominantly give 2-oxiranlymethyl-1,2,3-triazole 6e in 93% yield without the formation of nitrile 10 (entry 4). On the other hand, treatment of 5f, possessing gem-dimethyl group at the opposite side, with TfOH afforded ketone 11f through rapid hydride transfer (entry 5).

**Table 1.** Conversions of the various oxiranmethyl-1,2,3-triazole 5 to nitrile 10 and 2-oxiranlymethyl-1,2,3-triazoles 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product (yield)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5b</td>
<td>10 (51%)</td>
</tr>
<tr>
<td>2</td>
<td>5c</td>
<td>10 (73%)</td>
</tr>
<tr>
<td>3</td>
<td>5d</td>
<td>10 (60%)</td>
</tr>
<tr>
<td>4</td>
<td>5e</td>
<td>6e (93%)</td>
</tr>
<tr>
<td>5b</td>
<td>5f</td>
<td>11f (quant)</td>
</tr>
</tbody>
</table>

*Isolated yield. **Treatment with only TfOH (2 equiv)

These results led us to examine similar transformation using several analogues of 5e (Table 2). The conversion of 1-(oxiranamethyl)-1,2,3-triazole 5g possessing a phenyl group at the C2 position also smoothly proceeded to give 2-(oxiranamethyl)-1,2,3-triazole 6g in 97% yield (entry 1). The 1-
(oxiranylmethyl)-1,2,3-triazoles possessing a functional group such as methyl ether (5h), benzyl ether (5i), and chloride (5j) also afforded the desired products 6h, 6i, and 6j in 42%, 80%, and 57% yields, respectively (entries 2, 3, and 4). It was therefore confirmed that the novel conversion method from 1-(oxiranylmethyl)-1,2,3-triazoles to the corresponding 2-(oxiranylmethyl)-1,2,3-triazoles is applicable to various triazoles.

Table 2. Synthesis of the various 2-oxiranylmethyl-1,2,3-triazoles 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>NaH (equiv)</th>
<th>Time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-Ph (5g)</td>
<td>6.5</td>
<td>4</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>-CH2OMe (5h)</td>
<td>3.5</td>
<td>3.5</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>-(CH2)2OBn (5i)</td>
<td>5</td>
<td>6</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>-(CH2)2Cl (5j)</td>
<td>3.5</td>
<td>3</td>
<td>57</td>
</tr>
</tbody>
</table>

*aIsolated yield.

We were curious about the preferential formation of 2-(oxiranylmethyl)-1,2,3-triazole 6 rather than reformation of 1-(oxiranylmethyl)-1,2,3-triazole 5 from the alkoxy intermediate generated from bicyclic triazolium ion 9. The results indicate that the epoxide-forming reaction occurred through attack of the alkoxy moiety on the more sterically hindered carbon atom. With a view to obtaining information about general tendency for this type of reaction, the epoxide-forming reaction of a simple substrate was examined. Thus, 1,3-dihalo-3-methyl-2-butanol (12) was treated with potassium carbonate in deuterated methanol. The epoxide-forming reaction of 12 resulted in the formation of a 6:1 regioisomeric mixture in favor of tri-substituted oxirane 13 (Scheme 3). This result strongly suggested that the ring-closing reactions of alcohols possessing a β-leaving group tend to give multi-substituted epoxides despite the large steric hindrance at the reaction site. To our knowledge, this is the first example of the simple comparison of the reactivity between the tertiary and primary chlorides in epoxide ring-closing reaction.12

In conclusion, novel transformation of 1-(oxiranylmethyl)-1,2,3-triazoles 5 into alkanenitriles 10 or 2-oxiranylmethyl-1,2,3-triazoles 6 were discovered. The reaction pathway leading to 6 or 10 depends on the substituent pattern of the epoxide side chain. The present transformation of 5 into 6 provides a new entry for the synthesis of 2-substituted-1,2,3-triazoles.13,14

Acknowledgment

This work was partially supported by the Global COE program (Project No. B01: Catalysis as the Basis for Innovation in Material Science), Grant-in-Aid for Scientific Research (Grant No. 24310162), and Grant-in-Aid for Scientific Research on Innovative Areas (Project No. 2105: Organic Synthesis Based on Reaction Integration and No. 2301: Chemical Biology of Natural Products) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References


Scheme 3. Epoxide-forming reaction of 12.
One-pot click reaction of alkyl halide, see Kacprzak, K. Synlett. 2005. 6, 943-946.

4-Trimethyltriazole 5a was employed for the structural analysis of reactive intermediate cation 8a because corresponding butyl or phenyl compounds are insoluble amorphous material in CDCl3.

Other Brønsted and Lewis acids such as BF3·Et2O, Et3AlCl, TiCl4, Hg(OtO2)n, TFA could not activate the epoxide. However, TBSOTf and TMSOTf also gave the intermediate 8a due to in situ generated TiOH.

We confirmed that the internal 1,2,3-triazole ring is necessary for the ring opening reaction of oxirane leading to triflate alcohol 8. Treatment of oxirane 15 with 2.0 equiv of TfOH gave a complex mixture. Similar treatment in the presence of 1 equiv of triazole 16 also afforded the complex mixture.

Typical procedure for 1,2,3-triazole 11: Treatment of 5a with sodium hydride induced the ring opening reaction of epoxide to give a corresponding enaminoalcohol 17 in 23% yield, along with recovery of starting material 5a (70%).


(12) Typical procedure for the transformation of 5a into nitrile 10: To a solution of 5a (43 mg, 0.14 mmol) in CH2Cl2 (0.7 mL) was added TIOH (25 μL, 0.28 mmol) at 0 °C. After the mixture was stirred at room temperature for 30 min, t-BuOH (1 mL) was added. The mixture was stirred for 3 h and concentrated under reduced pressure to give crude 9a. To a suspension of NaH (21 mg, 0.49 mmol) in THF (0.5 mL) was added a solution of crude 9a in THF (2.3 mL) through a cannula at 0 °C. The mixture was stirred for 3.5 h, and the reaction was quenched with saturated aqueous NH4Cl solution. The mixture was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane/ethyl acetate 4/1) to give nitrile 10 (22 mg, 70%) as colorless oil. 9a: 1H NMR (500 MHz, CDCl3) δ 8.13 (s, 1H), 5.47 (br, 1H), 4.92 (dd, 1H, J = 14.0, 4.9 Hz), 4.86 (dd, 1H, J = 13.2, 5.2 Hz), 4.72 (dd, 1H, J = 13.7 Hz), 4.64 (dd, 1H, J = 13.2 Hz), 2.76 (t, 2H, J = 8.0 Hz), 1.70-1.84 (m, 2H), 1.36-1.26 (m, 20H), 0.87 (t, 3H, J = 6.9 Hz).

1H NMR (500 MHz, CDCl3) δ 7.38 (s, 1H), 4.55 (dd, 1H, J = 14.4, 6.3 Hz), 4.48 (dd, 1H, J = 14.3, 6.3 Hz), 3.23 (t, 1H, J = 6.0 Hz), 2.66 (t, 2H, J = 7.7 Hz), 1.68-1.62 (m, 2H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34-1.26 (m, 20H), 0.88 (t, 4H, J = 6.9 Hz), 1.36 (s, 3H), 1.34-1.26 (m, 20H), 0.88 (t, 4H, J = 6.9 Hz), 1.43 (s, 3H), 1.36 (s, 3H), 1.34-1.26 (m, 20H), 0.88 (t, 4H, J = 6.9 Hz).

11C NMR (CDCl3) δ 149.20, 133.00, 60.86, 58.65, 53.92, 31.88, 29.64, 29.62, 29.61, 29.59, 29.51, 29.32, 29.23, 29.21, 24.44, 23.72, 22.65, 18.86, 14.08; HRMS (EI) calc for (M+) 335.2936, found 335.2946. 6g: 1H NMR (500 MHz, CDCl3) δ 7.86 (s, 1H), 7.77 (d, 2H, J = 6.9 Hz), 7.41 (t, 2H, J = 7.4 Hz), 7.34 (t, 1H, J = 7.4 Hz), 4.64 (dd, 1H, J = 14.3, 5.7 Hz), 4.54 (dd, 1H, J = 14.3, 5.7 Hz), 3.29 (t, 1H, J = 5.7 Hz), 1.46 (s, 3H), 1.36 (s, 3H). 6h: 1H NMR (500 MHz, CDCl3) δ 7.54 (s, 1H), 4.51 (dd, 1H, J = 13.8, 5.8 Hz), 4.48 (s, 2H), 4.47 (dd, 1H, J = 14.3, 5.7 Hz), 3.34 (s, 3H), 3.18 (t, 1H, J = 5.7 Hz), 1.37 (s, 3H), 1.29 (s, 3H), 1.36 (s, 3H). 6i: 1H NMR (500 MHz, CDCl3) δ 7.37 (s, 1H), 7.34-7.37 (m, 5H), 4.53 (dd, 1H, J = 14.3, 5.8 Hz), 4.52 (s, 2H), 4.48 (dd, 1H, J = 14.3, 5.8 Hz), 3.53 (t, 2H, J = 6.3 Hz), 3.22 (t, 1H, J = 5.8 Hz), 2.79 (t, 2H, J = 5.7 Hz), 1.98 (m, 2H, J = 6.3 Hz), 1.43 (s, 3H), 1.36 (s, 3H). 6j: 1H NMR (500 MHz, CDCl3) δ 7.36 (s, 1H), 4.47 (dd, 1H, J = 14.3, 5.8 Hz), 4.44 (dd, 1H, J = 14.3, 5.7 Hz), 3.52 (t, 2H, J = 6.3 Hz), 3.16 (t, 1H, J = 5.7 Hz), 2.79 (t, 2H, J = 6.9 Hz), 2.08 (m, 2H, J = 6.3 Hz), 1.36 (s, 3H), 1.30 (s, 3H).