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

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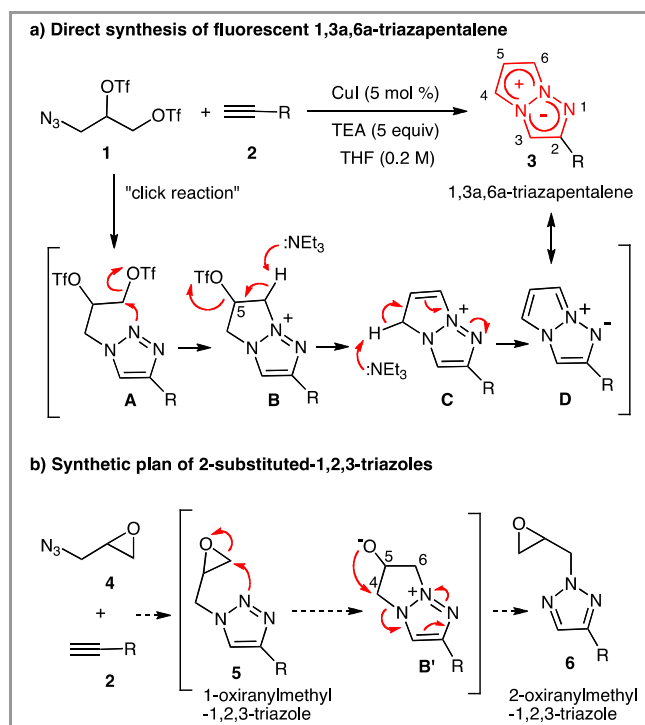
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Abstract: New reactions for transformation of 1-(oxiranylmethyl)-1,2,3-triazoles into 2-(oxiranylmethyl)-1,2,3-triazoles or alkanenitriles were established. Successive treatment of the substrate with triflic acid and *t*-BuOH afforded 4,6-dihydro-5-hydroxy-1,3a,6a-triazapentalene derivative. Under the influence of NaH, the bicyclic compound was converted to a 2-(oxiranylmethyl)-1,2,3-triazole or an alkanenitrile. 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.^{1,2} The reaction consists of Cu(I)-catalyzed azide/alkyne condensation to regioselectively provide 1-substituted-1*H*-1,2,3-triazoles under mild conditions, and a large number of 1-substituted-1*H*-1,2,3-triazole derivatives have been reported as useful compounds.³ In contrast, much less attention has been paid to 2-substituted-2*H*-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.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 alkyne and azide **1**.⁵ The click reaction of azide **1** 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.⁶ Based on these synthetic studies of 1,3a,6a-triazapentalenes, we newly planned the direct synthesis of 2-substituted-2*H*-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 alkyne would give 1-(oxiranylmethyl)-1,2,3-triazole **5** which may undergo a cyclization reaction to afford bicyclic triazolium ion

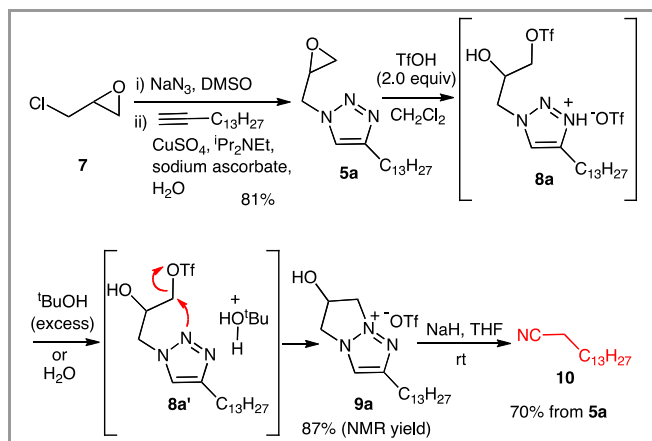
B'. The formation of alkoxide ion at **B'** would not induce the elimination to afford 1,3a,6a-triazapentalenes and reform the epoxide ring at C4 position to give 2-oxiranylmethyl-1,2,3-triazole **6** as depicted in scheme 1b. However, the alternative epoxide ring-closing mode at C6 position is also 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.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 an regioselective epoxide opening reaction.^{8,9} 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 oligomerization 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-oxylanymethyl-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



Scheme 2. Synthesis of 5-hydroxy-intermediate **9a** and its conversion to nitrile **10**.

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-oxiranymethyl-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 oxiranymethyl-1,2,3-triazole **5** to nitrile **10** and 2-oxiranymethyl-1,2,3-triazoles **6**.

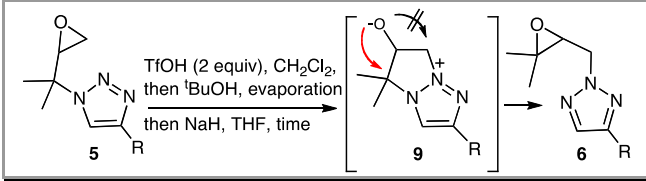
entry	substrate	product (yield) ^a
1		10 (51%)
2		10 (73%)
3		10 (60%)
4		 6e (93%)
5 ^b		 11f (quant)

^aIsolated yield. ^bTreatment with only TfOH (2 equiv)

These results led us to examine similar transformation using several analogues of **5e** (Table 2). The conversion of 1-(oxiranymethyl)-1,2,3-triazole **5g** possessing a phenyl group at the C2 position also smoothly proceeded to give 2-(oxiranymethyl)-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.

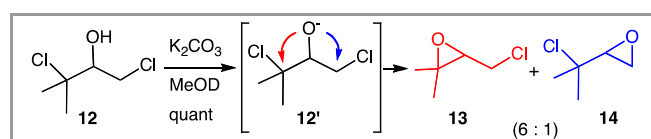
Table 2. Synthesis of the various 2-oxiranylmethyl-1,2,3-triazoles **6**.



Entry	R	NaH (equiv)	Time (h)	yield ^a (%)
1	-Ph (5g)	6.5	4	97
2	-CH ₂ OMe (5h)	3.5	3.5	42
3	-(CH ₂) ₃ OBn (5i)	5	6	80
4	-(CH ₂) ₃ Cl (5j)	3.5	3	57

^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 alkoxide intermediate generated from bicyclic triazolium ion **9**. The results indicate that the epoxide-forming reaction occurred through attack of the alkoxide ion 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-dichloro-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



Scheme 3. Epoxide-forming reaction of **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}

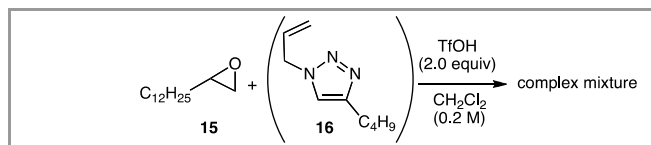
Acknowledgment

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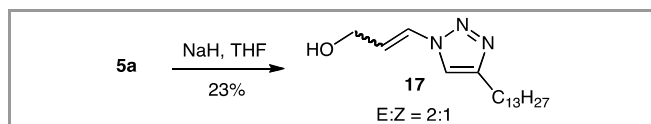
References

- (1) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599. (c) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
- (2) For review see: (a) Fan, W. Q.; Katritzky, A. R. In *Comprehensive Heterocyclic Chemistry II*. Vol. 4, Katritzky, A. R.; Rees, C. W.; Scriven, C. W. V. Eds.; Oxford, Elsevier, **1996**; pp. 1–126; (b) Hein, C. D.; Liu, X.-M.; Wan, D. *Pharmaceutical Research* **2008**, *25*, 2216–2230; (c) Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, 39, 675–696.
- (3) For recent reviews, see: (a) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449. (b) Kvivopalov, V. P.; Shkurko, O. P. *Russ. Chem. Rev.* **2005**, *74*, 339; (c) Bock, V. D.; Hiemstra, H.; Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *1*, 51–68; (d) Wu, P.; Fokin, V. V. *Aldrichimica Acta*, **2007**, *40*, 7–17.
- (4) For recent examples, see: (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786–7787; (b) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 2386–2393. (c) Kalisiak, J.; Sharpless, B.; Fokin, V. V. *Org. Lett.* **2008**, *10*, 3171–3174. (d) Chen, Y.; Liu, Y.; Petersen, J. L. Shi, X. *Chem. Commun.* **2008**, 3254–3256; (e) Liu, Y.; Yan, W.; Chen, Y.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 5389–5392. (f) Wang, X.-J.; Zhang, L.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *11*, 5026–5028. (g) Wang, X.-J.; Sidhu, K.; Zhang, L.; Campbell, S.; Haddad, N.; Reeves, D. C.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2009**, *23*, 5490–5493. (h) Yamauchi, M.; Miura, T.; Murakami, M. *Heterocycles*, **2010**, *80*, 177–181. (i) Wang, X.-J.; Zhang, L.; Krishnamurthy, D.; Senanayake, C. H.; Wipf, P. *Org. Lett.* **2010**, *12*, 4632–4635. (j) Ueda, S.; Su, M.; Buchwald, S. L.; *Angew. Chem. Int. Ed.* **2011**, *50*, 8944–8947. (k) Zhang, Y.; Li, X.; Li, J.; Chen, J.; Meng, X.; Zhao, M.; Chen, B. *Org. Lett.* **2012**, *14*, 26–29. (l) Guru, M. M.; Punniyamurthy, T. *J. Org. Chem.* **2012**, *77*, 5063–5073.
- (5) Namba, K.; Osawa, A.; Ishizaka, S.; Kitamura, N.; Tanino, K. *J. Am. Chem. Soc.* **2011**, *133*, 11466–11469.
- (6) Namba, K.; Mera, A.; Osawa, A.; Sakuda, E.; Kitamura, N.; Tanino, K. *Org. Lett.* **2012**, *14*, 5554–5557.

- (7) One-pot click reaction of alkyl halide, see Kacprzak, K. *Synlett*, **2005**, 6, 943-946.
- (8) 4-Tridecyl triazole **5a** was employed for the structural analysis of reactive intermediate cation **8a** because corresponding butyl or phenyl compounds are insoluble amorphous material in CDCl_3 .
- (9) Other Brønsted and Lewis acids such as $\text{BF}_3 \cdot \text{Et}_2\text{O}$, Et_2AlCl , TiCl_4 , $\text{Hg}(\text{OTf})_2$, TFA could not activate the epoxide. However, TBSOTf and TMSOTf also gave the intermediate **8a** due to in situ generated TfOH.
- (10) 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.



- (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) (a) The comparison of halogen atoms in the epoxide ring-closing reaction of 2,2,6,6-tetrahalogenocyclohexanols, see Duhamel, P.; Leblond, B.; Bidois-Séry, L.; Poirier, J.-M.; *J. Chem. Soc., Perkin Trans. 1*, **1994**, 16, 2265-2271. (b) Epoxide-forming reaction of 2-chloro-1-(1-chlorocyclopropyl)ethanol, see WO 2011070742.
- (13) Typical procedure for the transformation of **5a** into nitrile **10**: To a solution of **5a** (43 mg, 0.14 mmol) in CH_2Cl_2 (0.7 mL) was added TfOH (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 NH_4Cl solution. The mixture was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over MgSO_4 , 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, CDCl_3) 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 (d, 1H, $J = 13.7$ Hz), 4.64 (d, 1H, $J = 13.2$ Hz), 2.76 (t, 2H, $J = 8.0$ Hz), 1.70-1.64 (m, 2H), 1.36-1.26 (m, 20H), 0.87 (t, 3H, $J = 6.9$ Hz).
- (14) The transformation of 1-(Oxiranylmethyl)-1,2,3-triazoles **5** into 2-(Oxiranylmethyl)-1,2,3-triazoles **6** is conducted in the same manner as above typical procedure. **6e**: White amorphous; ^1H NMR (500 MHz, CDCl_3) 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); ^{13}C NMR (CDCl_3 , 125.8 MHz) 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, 25.44, 24.37, 22.65, 18.86, 14.08; HRMS (EI) calcd for (M^+) 335.2936, found 335.2946. **6g**: ^1H NMR (500 MHz, CDCl_3) 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, CDCl_3) 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, CDCl_3) δ 7.37 (s, 1H), 7.34-7.27 (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 (qn, 2H, $J = 6.3$ Hz), 1.43 (s, 3H), 1.36 (s, 3H). **6j**: ^1H NMR (500 MHz, CDCl_3) 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 (qn, 2H, $J = 6.3$ Hz), 1.36 (s, 3H), 1.30 (s, 3H).