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Indium(III) triflate catalyzed tandem azidation/1,3-dipolar cycloaddition reaction of ω,ω-dialkoxyalkyne derivatives with trimethylsilyl azide

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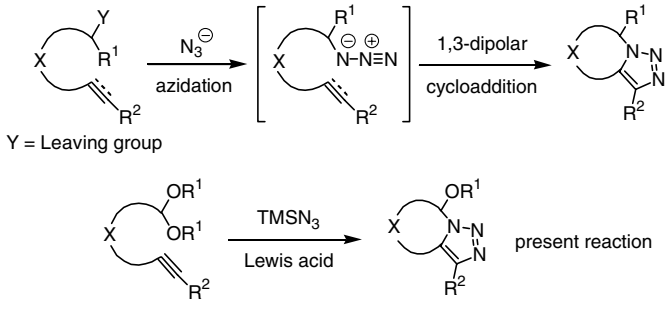
Abstract—The azidation reaction of dialkyl acetal derivatives with trimethylsilyl azide ($TMSN_3$) was efficiently catalyzed by 1–5 mol % of $In(OTf)_3$. The major product differed depending on the substrate structure and molar ratio of $TMSN_3$, that is, aliphatic acetals provided α-azido ether derivatives, while aromatic acetal (benzaldehyde dimethyl acetal) provided *gem*-diazide, respectively. Furthermore, novel tandem azidation/1,3-dipolar cycloaddition reaction using alkynyl acetal derivatives gave bicyclic triazolo-heterocyclic compounds, recognized as chemically modified aza-sugar analogues, in high yields under mild conditions.

1. Introduction

Recently, 1,2,3-triazolo-heterocyclic compounds, in particular sugar analogues having triazole moiety, are attracting much attention in medicinal chemistry field. This is due to the fact that oligosaccharides play important roles in many cellular functions[1] and some of this class of compounds have been reported to possess interesting inhibitory activities against glycosidases.[2,3] For the synthesis of these triazole modified sugar derivatives,[4,5] copper-catalyzed cycloaddition reaction of azide with an acetylenic compound is an efficient method, which is well known as a typical example of 'click chemistry'.[6,7] Most of such copper-catalyzed reactions so far reported are intermolecular versions,[6b,7] although an intramolecular reaction should provide a powerful method for the synthesis of structurally different analogues difficult to obtain by an intermolecular reaction, in particular polycyclic fused triazole derivatives. Preparation of an azide compound from unsaturated sulfonate and NaN_3 followed by thermal intramolecular cycloaddition has been known as a conventional protocol (Scheme 1).[8] However, since most of the reported examples have employed alkene moiety as a dipolarophile, thereby



Scheme 1.

Keywords: Indium(III) triflate; Azidation; 1,3-Dipolar cycloaddition; Tandem reaction; Triazolo-heterocyclic compounds.
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resulting in the formation of unstable triazolin derivatives, product yields did not always meet at the expected levels. Low yield in the conversion of triazolin into triazole usually achieved by base or oxidizing reagent has also been a problem to be solved. Moreover, due to the thermally labile nature of organic azide compounds, it is desirable for the reaction to proceed under mild conditions.

According to one of our ongoing research projects, we have been developing new synthetic methods using conceptually unique Lewis acids. We have reported on novel bidentate Lewis acids[9,10] or indium(III) triflate [$In(OTf)_3$] in aqueous media[11] for intramolecular Diels–Alder reactions of ester-tethered substrates. Further studies were undertaken to develop Lewis acid catalyzed tandem azidation and 1,3-dipolar cycloaddition of unsaturated acetal compounds with $TMSN_3$.[12,13] In this letter, we report that efficient tandem azidation and 1,3-dipolar cycloaddition reaction of various ω,ω-dialkoxy alkyne derivatives leading to the achievement of the fused triazole derivatives by the use of $In(OTf)_3$ as a Lewis acid.

2. Azidation of dimethyl acetal derivatives

Using 1,1-dimethoxyhexane **1a** and $TMSN_3$ as model substrates, azidation reaction was conducted in the presence of various Lewis acids (Table 1). As shown in entry 1, in the presence of 1 mol % $In(OTf)_3$, reaction of **1a** with 1.1 equiv $TMSN_3$ in CH_2Cl_2 proceeded at room temperature within 7 h to give α-azido ether **2a** along with the formation of a small amount of *gem*-diazide **3a** (81% yield, **2a**:**3a** = >20:1). Increase in molar ratio of $TMSN_3$ to 2 equiv resulted in shortening the reaction period (3 h at room temperature) and higher product yield of **2a** (91%), while any appreciable increase in the *gem*-diazide **3a** was not observed (entry 2). $InCl_3$, $Sc(OTf)_3$ and $Yb(OTf)_3$ showed similar catalytic activities to that of $In(OTf)_3$, but under similar conditions $Bi(OTf)_3$ resulted in a somewhat lower yield of **2a** (entries 3–5 vs 6). While aliphatic acetal **1a** gave α-azido ether **2a** highly predominantly, in the case of aromatic acetal **1b** ratio of *gem*-diazide compound **3b** over mono-azide **2b** increased depending on the amount of $TMSN_3$ used. That is, reaction of **1b** with 1.1 equiv of $TMSN_3$ catalyzed by 0.5 mol % $In(OTf)_3$ provided a mixture of **2b** and **3b** in 44% yield, and the mono-azide **3b** was the major product (**2b**:**3b** = 3.3:1, entry 7). However, as shown in entry 9, an excellent yield and highly selective formation of *gem*-diazide **3b** was observed in the reaction with 2.0 equiv $TMSN_3$ and 1 mol % $In(OTf)_3$.

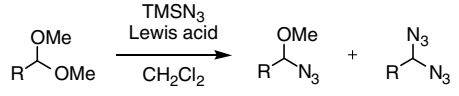
3. Tandem azidation/1,3-dipolar cycloaddition reaction

As mentioned above, selective mono-azidation efficiently proceeded in $In(OTf)_3$ catalyzed reaction of aliphatic acetal with $TMSN_3$ giving rise to α-azido ether derivative. Based on these results, to develop tandem azidation/1,3-dipolar cycloaddition reaction, we examined the reaction of $TMSN_3$ with ω,ω-dialkoxyalkyne derivatives having an aliphatic acetal moiety and 1,3-dipolarophile moiety. Results are summarized in Table 2.

In the presence of 5 mol % $In(OTf)_3$, reaction of $TMSN_3$ (1.5 equiv) with dimethylacetal having ynone moiety **4a** (R = COPh) was conducted at room temperature for 30 min, then at 50 °C for 3 h providing triazolopyridine derivative **5a** in 75% yield (entry 1) (Fig. 1).[14] As a Lewis acid, $Sc(OTf)_3$ and $Bi(OTf)_3$ were found to be as effective as $In(OTf)_3$ (entries 3 and 4). Contrary to these, $InCl_3$ or $Yb(OTf)_3$ worked less effectively to give the product **5a** in moderate yields, 48% and 43%, respectively, along with the recovery of **4a** (entries 2 and 5). From these results and due to its moisture-insensitive and thermally stable nature as well as its relatively low price, we used $In(OTf)_3$ in the following experiments.[15]

To see the substituent effect on the reactivity, such substrates having alkanoyl, ester, hydrogen and trimethylsilyl group on the acetylenic moiety **4b–f** were used.

Table 1. Lewis acid catalyzed azidation of acetal derivatives (**1a**,**b**) with $TMSN_3$

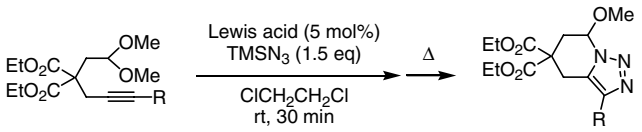


1a: R = *n*-C_5H_{11}
1b: R = Ph
2
3

Entry	1	Lewis acid (mol %)	$TMSN_3$ (equiv)	Temperature (°C)	Time (h)	Yield[a] (%)	Ratio[b] (**2**:**3**)
1	**1a**	$In(OTf)_3$ (1.0)	1.1	rt	7	81	>20:1
2	**1a**	$In(OTf)_3$ (1.0)	2.0	rt	3	91[c]	>20:1
3	**1a**	$InCl_3$ (1.0)	2.0	rt	7	79	>20:1
4	**1a**	$Sc(OTf)_3$ (1.0)	2.0	rt	7	83	>20:1
5	**1a**	$Yb(OTf)_3$ (1.0)	2.0	rt	7	79	>20:1
6	**1a**	$Bi(OTf)_3$ (1.0)	2.0	rt	7	59	>20:1
7	**1b**	$In(OTf)_3$ (0.5)	1.1	0	2	44[c]	3.3:1
8	**1b**	$In(OTf)_3$ (0.5)	2.0	0	2	70[c]	1:4.6
9	**1b**	$In(OTf)_3$ (1.0)	2.0	0	2	98[c]	1:8.2

[a] Yield was calculated by ^1H NMR.
[b] Ratio of mono-azide **2** and *gem*-diazide **3** was determined by ^1H NMR.
[c] Isolated yield.

Table 2. Tandem azidation/1,3-dipolar cycloaddition reaction of diethyl malonates (**4**) with $TMSN_3$



4 **5**

Entry	**4**	R	Lewis acid	Temperature (°C)	Time (h)	**5**	Yield[a] (%)
1	**4a**	COPh	$In(OTf)_3$	50	3	**5a**	75
2	**4a**	COPh	$InCl_3$	50	3	**5a**	48[b]
3	**4a**	COPh	$Sc(OTf)_3$	50	3	**5a**	78
4	**4a**	COPh	$Bi(OTf)_3$	50	3	**5a**	73
5	**4a**	COPh	$Yb(OTf)_3$	50	3	**5a**	53[c]
6	**4b**	$COCH_2CH_2Ph$	$In(OTf)_3$	50	4	**5b**	81
7	**4c**	CO_2Et	$In(OTf)_3$	50	9	**5c**	72
8	**4d**	H	$In(OTf)_3$	70	48	**5d**	72
9	**4e**	$SiMe_3$	$In(OTf)_3$	70	20	**5e**	93
10	**4f**	CF_2Br	$In(OTf)_3$	50	8	**5f**	38[d]
11	**4f**	CF_2Br	$In(OTf)_3$	rt	36	**5f**	60

[a] Isolated yield.
[b] Recovery of **4a**, 37%.
[c] Recovery of **4a**, 32%.
[d] Complex mixture was obtained.

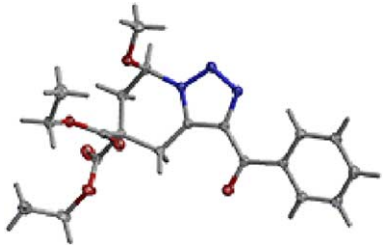


Figure 1. X-ray structure of **5a**.

Under the similar conditions for **4a** (entry 1), the alkanoyl derivative **4b** ($R = COCH_2CH_2Ph$) showed similar reactivity to give the cyclized product **5b** in 81% yield (entry 6). The ester derivative **4c** ($R = CO_2Et$) showed lower reactivity requiring a longer reaction time (50 °C, 9 h), to give the cyclized product **5c** in 72% yield (entry 7).

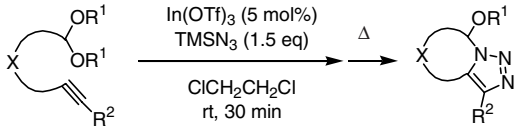
Compared to the substrates **4a–c** having an electron deficient 1,3-dipolarophile part, the reactivity of terminal alkyne **4d** (R = H) and TMS-substituted substrate **4e** ($R = SiMe_3$) decreased so much that a higher temperature and much longer reaction time were needed. That is, after 48 h at 70 °C, **4d** gave the cyclized product **5d** in 72% yield and **4e** gave **5e** in 93% yield after 20 h at 70 °C (entries 8 and 9). It is well documented that introduction of fluorine atom into molecules often exerts an increase in biological activity or enhancement of lipophilicity. We examined the reaction using bromodifluoromethylated substrate **4f**, since this group in the product **5f** would be expected to be utilized for further elaboration of a variety of fluorinated derivatives. When optimized reaction conditions (50 °C) were employed, reaction proceeded rather sluggishly to give the cyclized product **5f** in only 38% yield. Although it took a longer period (36 h), room temperature reaction provided **5f** in reasonable yield (60%, entries 10 and 11).

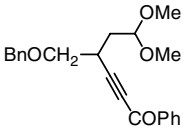
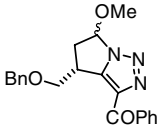
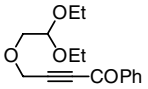
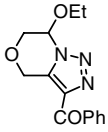
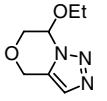
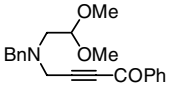
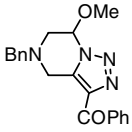
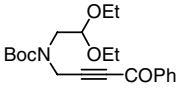
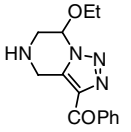
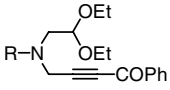
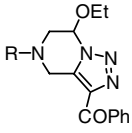
Next we examined the effect of tether moiety linking dimethyl acetal part and ynone part. Results are summarized in Table 3. Compared to substrate **4a**, the reaction of one carbon-shortened substrate **4g** at 50 °C for 3 h gave the cyclized product **5g** in 71% yield accompanying the formation of unidentified side products. Improvement was not realized by lowering the reaction temperature (room temperature) to give **5g** in only 21% yield. In both cases, the diastereomer ratio was 1.3:1 consisting of trans isomer as a major isomer determined by 2D NMR experiment (^1H–^1H COSY, HSQC, HMBC and NOESY) (Scheme 3).[16]

Ether tethered substrates **6a** and **6b** also reacted smoothly to give triazolooxazine derivatives **7a**,**b** in good yield (entries 3 and 4). It is noted that terminal alkyne substrate **6b** reacted much faster than the malonate derivatives **4b** shown in Table 2 (70 °C, 48 h, 72% from **4b** to **5b** vs 50 °C, 17 h, 75% from **6b** to **7b**). Three types of amino-tethered substrates **8a**,**b** and **8c–d** were employed. *N*-Benzyl derivative **8a** had a disappointing result to give the cyclized product **9a** in only a trace amount, instead, several side reactions including 1,4-addition of azide to ynone moiety predominantly occurred (entry 5).[17] In the case of *N*-Boc derivative **8b**, the removal of the Boc group was also accompanied during the tandem reaction giving rise to the amino-free triazolopyridine derivative **9′** in 39% yield (entry 6). Reaction with *N*-tosyl derivative **8c** proceeded smoothly to give the cyclized product **9c** in 87% yield (entry 7). Likewise, *N*-4-nitrobenzenesulfonyl derivative **9d** gave an essentially similar result (entry 8).

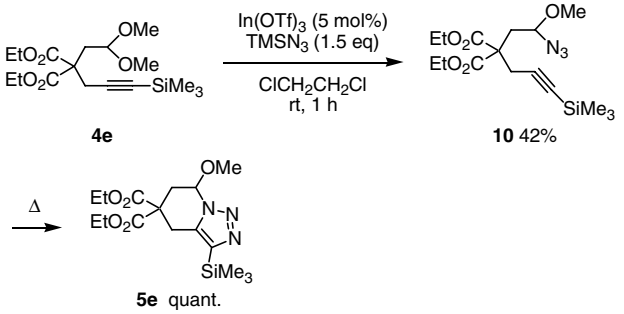
Regarding the reaction pathway, the present tandem reaction possibly involves $In(OTf)_3$ catalyzed formation of α-azido ether followed by the intramolecular 1,3-dipolar cycloaddition to give fused triazolo derivatives. As shown in Scheme 2, α-azido ether **10** was isolated

Table 3. Tandem azidation/1,3-dipolar cycloaddition reaction of various ω,ω-dialkoxyalkynes with $TMSN_3$

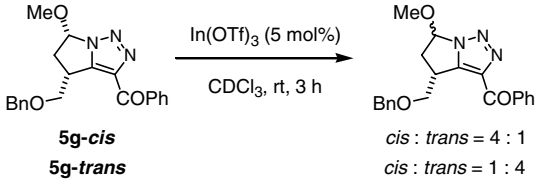


Entry	Substrates (**4**, **6**, **8**)		Temperature (°C)	Time (h)	Products (**5**, **7**, **9**)		Yield[a] (%)	dr[b]
1		**4g**	50	3		**5g**	71	1.3:1
2		**4g**	rt	48		**5g**	21	1.3:1
3		**6a**	50	2		**7a**	83	—
4		**6b**	50	17		**7b**	75	—
5		**8a**	70	48		**9a**	Trace[c]	—
6		**8b**	50	12		**9b**	39	—
7		**8c** R = Ts	50	4		**9c**	87	—
8		**8d** R = 4-Ns	50	4		**9d**	87	—

[a] Isolated yield.
[b] Ratio of diastereomers was determined by ^1H NMR of the crude mixture.
[c] Michael addition product was isolated in 28% yield.



Scheme 2.



Scheme 3.

when the azidation reaction was conducted at room temperature.

Upon heating this isolated azide derivative **10** (70 °C, 20 h), cyclized product **5e** was formed in a quantitative yield.

In conclusion, we found that the azidation reaction of dialkoxy acetal derivatives with $TMSN_3$ is efficiently catalyzed by 1–5 mol % of $In(OTf)_3$. Using a variety of ω,ω-dialkoxy acetylenic compounds as a substrate, bicyclic 1,2,3-tirazolo-heterocyclic compounds could be obtained in good yield through sequential azidation and the intramolecular 1,3-dipolar cycloaddition reaction. The present tandem reaction provides a convenient and general method for the preparation of triazole-fused cyclic compounds, some of which could be applied as aza-sugar analogues.

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11. Yanai, H.; Saito, A.; Taguchi, T. *Tetrahedron* **2005**, *61*, 7087.
12. (a) Kirchmeyer, S.; Mertens, A.; Olah, G. A. *Synthesis* **1983**, 500; (b) Nishiyama, K.; Oba, M.; Watanabe, A. *Tetrahedron* **1987**, *43*, 693; (c) Richard, J. P.; Amyes, T. L.; Jagannadham, V.; Lee, Y.-G.; Rice, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 5198.
13. (a) Hassner, A.; Fibiger, R.; Amarsekara, A. S. *J. Org. Chem.* **1988**, *53*, 22; (b) Kim, S.; Park, J. H.; Lee, S. *Tetrahedron Lett.* **1989**, *30*, 6697.
14. *Typical procedure*: To a suspension of $In(OTf)_3$ (5.6 mg, 10 μmol) in 1,2-dichloroethane (1.5 mL), $TMSN_3$ (41 μL, 0.35 mmol) and a solution of **4a** (79.3 mg, 0.20 mmol) in 1,2-dichloroethane were added at room temperature. After being stirred for 30 min, the resulting mixture was stirred for 3 h at 50 °C. The reaction mixture was quenched by H_2O (3 mL) and extracted with $CHCl_3$ (3 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 3:1) to give diethyl 3-benzoyl-7-methoxy-6,7-dihydro[1,2,3]triazolo[1,5-*a*]pyridine-5, 5(4*H*)-dicarboxylate **5a** (60.0 mg, 0.15 mmol, 75% yield) as colourless crystals. Mp 101.5 °C. IR (KBr) ν cm^{-1}; 2982, 1737, 1648, 1475, 1234. ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (3H, t, $J = 7.1$ Hz), 1.25 (3H, t, $J = 7.1$ Hz), 2.62 (1H, dd, $J = 14.7$, 4.1 Hz), 2.43 (1H, ddd, $J = 14.7$, 2.6, 1.0 Hz), 3.26 (1H, d, $J = 18.6$ Hz), 3.57 (3H, s), 4.13–4.28 (5H, m), 5.77 (1H, dd, $J = 3.8$, 3.0 Hz), 7.48 (2H, t, $J = 8.1$ Hz), 7.55–7.60 (1H, m), 8.41 (2H, br d, $J = 8.1$ Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.7, 13.8, 27.8, 33.9, 49.5, 58.1, 62.0, 62.3, 85.6, 128.2, 130.5, 132.9, 136.9, 138.1, 142.4, 169.1, 169.6, 186.6. ESI-MS *m*/*z*: 402 $[M+H]^+$. HRMS calcd for $C_{20}H_{24}N_3O_6$ $[M+H]^+$: 402.1665. Found: 402.1689. The structure of **5a** was confirmed by X-ray crystallographic analysis (Fig. 1). Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 284177. Copies of the data can be obtained, free of charge, on application to the Director, CCDC (e-mail: deposit@ccdc.cam.ac.uk).
15. It has been reported that $Bi(OTf)_3$ is moisture sensitive under thermal conditions: Repichet, S.; Zwick, A.; Vendier, L.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **2002**, *43*, 993.
16. Each isomer **5g-*cis*** or **5g-*trans*** was treated with $In(OTf)_3$ in $CDCl_3$ for 3 h at room temperature to reveal that the epimerization of *N*,*O*-acetal moiety occurs to some extent. That is, under these conditions **5g-*cis*** gave a 4:1 mixture of the *cis*/*trans* isomer, while **5g-*trans*** gave a *cis*/*trans* mixture in a ratio of 1:4. These results indicate that $In(OTf)_3$ can catalyze the epimerization of *N*,*O*-acetal moiety of the cyclized product **5g** (Scheme 3).
17. It was reported that γ-alkoxy α,β-ynoate derivatives are highly reactive substrates for 1,4-addition with N_3 anion: Laksmipathi, P.; Rao, A. V. R. *Tetrahedron Lett.* **1997**, *38*, 2551, in fact, the reaction of *N*-benzyl substrate **8a** and $TMSN_3$ without $In(OTf)_3$ gave the 1,4-adduct in 61% yield (70 °C, 48 h).