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1,3-Dipolar cycloaddition of alkynyliodonium salts with a nitrile oxide. Synthesis and reactivity of isoxazolyliodonium salts

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Abstract

1,3-Dipolar cycloaddition reaction of alkynyliodonium salts with 2,4,6-trimethylbenzonitrile *N*-oxide has been examined with respect to inactivated alkynyliodonium salts. The cycloaddition with the nitrile oxide has been found to proceed successful to give the corresponding isoxazolyliodonium salts in good to high yields. The reactivity of the selected isoxazolyliodonium salts has been examined.

Keywords: 1,3-Dipolar cycloaddition; Alkynyliodonium salt; Nitrile oxide; Isoxazolyliodonium salt

1. Introduction

Alkynyliodonium salts are useful compounds in organic chemistry because they have carbon–carbon triple bonds available for mechanistic and synthetic purposes [1]. Recently, the electron-deficient nature of the alkynyl moiety has been applied to cycloaddition reactions. Stang has extensively explored the Diels–Alder reactions of alkynyliodonium salts that have additional electron-withdrawing groups at the β position [2].

1,3-Dipolar cycloaddition is one of the useful methods for synthesizing heterocycles [3]. However, only few examples are reported in the literatures on the 1,3-dipolar cycloaddition of alkynyliodonium salts. Varvoglis and coworkers have reported the first 1,3-dipolar cycloaddition of arylethynyl(phenyl)iodonium salts with nitrile oxides and a nitrone [4]. Maas and Stang have developed the 1,3-dipolar cycloaddition to the β-activated ethynyl(phenyl)iodonium salts [5], involving the reactions with diazoketones and azides. Very recently, Stang and Murch have reported the 1,3-dipolar cycloaddition with a diazoester, a nitrone and a nitrile oxide [6].

However, the reported reactions are limited to the alkynyliodonium salts with aryl and β-activated groups. Thus, we report here the 1,3-dipolar cycloaddition of different types of alkynyliodonium salts, that is, alkyl and silyl groups, in the case of 2,4,6-trimethylbenzonitrile *N*-oxide as the 1,3-dipole. The cycloadducts derived from arylethynyliodonium salts resist against the nucleophilic substitution [4], while those derived from β-activated ethynyliodonium salts readily undergo the loss of the iodonium moiety [6]. The reactivity of the cycloadduct still remains unclear.

2. Results and discussion

2.1. 1,3-Dipolar cycloaddition of (phenyl)[(trimethylsilyl)ethynyl]iodonium triflate (1a) with 2,4,6-trimethylbenzonitrile N-oxide (2)

We examined the cycloaddition reaction of (phenyl)[(trimethylsilyl)ethynyl]iodonium triflate (**1a**) and 2,4,6-trimethylbenzonitrile *N*-oxide (**2**). Compound **2** was selected as a stable nitrile oxide to be able to conduct the cycloaddition reaction conveniently. When a mixture of (trimethylsilyl)iodonium triflate (**1a**) and nitrile oxide (**2**) was reacted in CH_2Cl_2 at room temperature, (phenyl)[3-(2,4,6-trimethylphenyl)-5-(trimethylsi-

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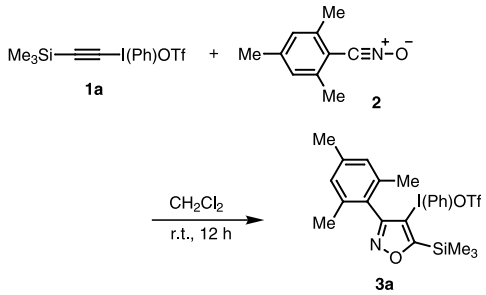
lyl)isoxazol-4-yl]iodonium triflate (**3a**) was formed as crystals in 91% yield (Eq. (1)). The cycloaddition reaction proceeded smoothly at room temperature to give the high yield of single cycloadduct **3a**. The structure of the cycloadduct **3a** was confirmed by the spectral data and elemental analysis and is consistent with the related isoxazolyliodonium salts [4]. The NOE experiment supported the regiochemistry of the cycloadduct **3a**. The irradiation of the *ortho* methyl of mesityl group showed the enhancement (1.2%) of the *ortho* proton of phenyl group, but no enhancement was observed at the signal of trimethylsilyl group.



(1)

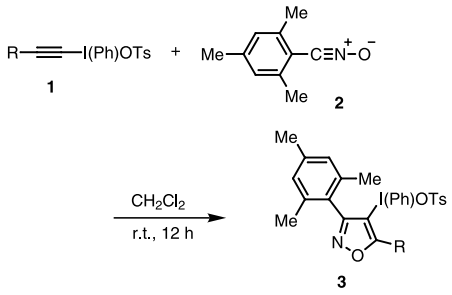
2.2. 1,3-Dipolar cycloaddition of alkynyl(phenyl)iodonium tosylates (*1*) with 2,4,6-trimethylbenzonitrile N-oxide (*2*)

As the trimethylsilylethynyliodonium salt (**1a**) underwent smoothly the cycloaddition with 2,4,6-trimethylbenzonitrile *N*-oxide (**2**), we examined the cycloaddition of alkyl-substituted ethynyliodonium tosylates **1**. When the iodonium tosylates **1** were reacted with **2** under the same reaction conditions as above, (phenyl)[5-alkyl-3-(2,4,6-trimethylphenyl)isoxazol-4-yl]-iodonium tosylates (**3**) were obtained in good to high yields, respectively (Eq. (2)). There seems to be no difference between the counteranions, triflate and tosylate. Therefore, the 1,3-dipolar cycloaddition of alkynyliodonium salts with a nitrile oxide provides a good methodology for preparing the isoxazolyliodinium salts (Table 1).

Table 1
Cycloaddition of alkynyl(phenyl)iodonium tosylates (**1**) with 2,4,6-trimethylbenzonitrile *N*-oxide (**2**)

Entry	Iodonium salt **1**	Product **3**	Yield (%) [a]
1	**1b**, $R = Bu$	**3b**, $R = Bu$	80
2	**1c**, $R = Hex$	**3c**, $R = Hex$	73
3	**1d**, $R = Dec$	**3d**, $R = Dec$	43
4	**1e**, $R = t$-Bu	**3e**, $R = t$-Bu	83
5	**1f**, $R = Ph$	**3f**, $R = Ph$	72

[a] Isolated yields based on alkynyl(phenyl)iodonium tosylates (**1**).

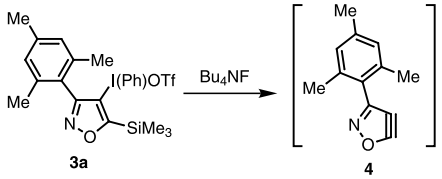


(2)

2.3. Reaction of isoxazolyliodonium salts *3*

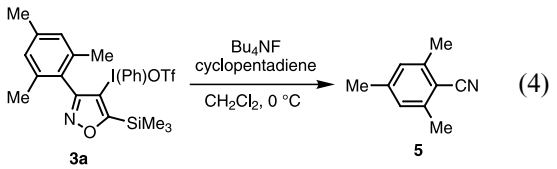
Although Varvoglis and coworkers reported the reaction of aryl-substituted isoxazolyliodonium tosylates **3** with some nucleophiles [4], the displacement of phenyliodonio group by the nucleophile was not observed. We also examined the substitution reaction of isoxazolyliodonium tosylates **3** with potassium thiocyanate, KSCN, but could not obtain any substitution products.

Recently, we have found that reaction of (phenyl)[2-(trimethylsilyl)phenyl]iodonium triflate with Bu_4NF generates benzyne efficiently under very mild conditions to give the benzyne adduct with furan quantitatively [7]. [3-(2,4,6-Trimethylphenyl)-5-(trimethylsilyl)isoxazol-4-yl]iodonium triflate (**3a**) has the similar structure bearing trimethylsilyl and phenyliodonio groups at two adjacent positions on the isoxazole ring. If the reaction of isoxazolyliodonium triflate (**3a**) proceeds in a similar manner to the benzyne formation, the generation of 4,5-didehydro-5-(2,4,6-trimethylphenyl)isoxazole (**4**) is expected (Eq. (3)). Thus, we examined the reaction of isoxazolyliodonium triflate (**3a**) with Bu_4NF.



(3)

Treatment of isoxazolyliodonium triflate (**3a**) with Bu_4NF in the presence of cyclopentadiene in CH_2Cl_2 gave 2,4,6-trimethylbenzonitrile (**5**) in 86% yield together with almost quantitative amount of iodobenzene (Eq. (4)). No cycloadducts derived from 4,5-didehydroisoxazole (**4**) and cyclopentadiene were detected. Attempted trapping reactions of didehydroisoxazole **4** with some agents such as furan, 1,3-diphenylisobenzofuran and tetraphenylcyclopentadienone were failed. Only benzonitrile **5** was formed as the product derived from the isoxazole component. This result suggests that an isoxazolyl anion generated by desilylation with fluoride ion undergoes the ring-cleavage [8] to benzonitrile **5** without generating a high strained 4,5-dedihydroisozazole.



(4)

3. Experimental

3.1. Measurements and materials

Melting points were measured with a YANACO micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a JEOL JNM-A SERIES FT-NMR (300 MHz) spectrometer, and chemical shifts (δ) were expressed in part per million downfield from tetramethylsilane. ^{13}C-NMR spectra were recorded on a JEOL JNM-A SERIES FT-NMR (75 MHz) spectrometer, and chemical shifts (δ) were expressed in part per million downfield from tetramethylsilane. Elemental analyses were performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

(Phenyl)[(trimethylsilyl)ethynyl]iodonium triflate (**1a**) [9] and alkynyl(phenyl)iodonium tosylates **1b**–**f** [10] were prepared according to the literature method. 2,4,6-Trimethylbenzonitrile *N*-oxide (**2**) was prepared by the method described in the literature [11]. Other materials were commercially available and used without further purification.

3.2. Reaction of phenyl(trimethylsilylethynyl)iodonium triflate (1a) with 2,4,6-trimethylbenzonitrile N-oxide (2)

A solution of phenyl(trimethylsilylethynyl)iodonium triflate (**1a**) (2.0 mmol) and 2,4,6-trimethylbenzonitrile *N*-oxide (**2**) (2.4 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature (r.t.) under nitrogen with protection from daylight for 12 h. The solvent was removed in vacuo and Et_2O was added to give the precipitation of (phenyl)[3 - (2,4,6 - trimethylphenyl) - 5 - (trimethylsilyl)-isoxazol-4-yl]iodonium triflate (**3a**) (1.11 g, 91%): m.p. 176–178 °C; ^{1}H-NMR ($CDCl_3$) δ 0.64 (s, 9H, $SiCH_3$), 1.70 (s, 6H, Me), 2.38 (s, 3H, Me), 6.91 (s, 2H, ArH), 7.25–7.58 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ −1.38, 19.56, 21.27, 92.17, 114.24, 119.76, 119.77, 128.73, 131.44, 132.32, 135.15, 137.95, 140.55, 161.90, 185.79. Anal. Calc. for $C_{22}H_{25}F_3INO_4SSi$: C, 43.21; H, 4.12; N, 2.29. Found: C, 43.19; H, 4.12; N, 2.33%.

3.3. General procedure for the reaction of alkynyl(phenyl)iodonium tosylates (1) with 2,4,6-trimethylbenzonitrile N-oxide (2)

A solution of alkynyliodonium tosylate (**1**) (1.0 mmol) and 2,4,6-trimethylbenzonitrile *N*-oxide (**2**) (1.2 mmol) in CH_2Cl_2 (10 ml) was stirred at r.t. under nitrogen with protection from daylight for 12 h. The solvent was removed in vacuo and Et_2O was added to give the precipitation of isoxazolyliodonium tosylate (**3**).

3.3.1. [5-Butyl-3-(2,4,6-trimethylphenyl)isoxazol-4-yl](phenyl)iodonium tosylate (3b)

Compound **3b**: 0.495 g (80%); m.p. 194–195 °C (CH_2Cl_2–hexane); ^{1}H-NMR ($CDCl_3$) δ 0.95 (t, $J = 7.4$ Hz, 3H, Me), 1.35–1.47 (m, 2H, CH_2), 1.66 (s, 6H, Me), 1.76–1.84 (m, 2H, CH_2), 2.30 (s, 3H, Me), 2.35 (s, 3H, Me), 3.14 (t, $J = 7.7$ Hz, 2H, CH_2), 6.84 (s, 2H, ArH), 6.97–7.15 (m, 4H, ArH), 7.29–7.46 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.70, 19.47, 21.20 (two signals overlapped), 22.37, 27.07, 29.15, 85.51, 116.38, 122.97, 125.66, 128.27, 128.45, 130.60, 131.14, 135.24, 137.79, 139.39, 139.96, 141.85, 162.89, 179.06. Anal. Calc. for $C_{29}H_{32}INO_4S$: C, 56.40; H, 5.22; N, 2.27. Found: C, 56.37; H, 5.19; N, 2.26%.

3.3.2. [5-Hexyl-3-(2,4,6-trimethylphenyl)isoxazol-4-yl](phenyl)iodonium tosylate (3c)

Compound **3c**: 0.469 g (73%); m.p. 202–204 °C (CH_2Cl_2–hexane); ^{1}H-NMR ($CDCl_3$) δ 0.86–0.90 (m, 3H, Me), 1.18–1.39 (m, 6H, CH_2), 1.64 (s, 6H, Me), 1.75–1.85 (m, 2H, CH_2), 2.29 (s, 3H, Me), 2.33 (s, 3H, Me), 3.10–3.15 (m, 2H, CH_2), 6.82 (s, 2H, ArH), 6.94–7.08 (m, 4H, ArH), 7.18–7.41 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 13.89, 19.40, 21.12 (two signals overlapped), 22.38, 27.02, 27.30, 28.90, 31.28, 85.52, 116.28, 122.95, 125.62, 128.21, 128.38, 130.50, 131.06, 135.20, 137.74, 139.30, 139.87, 141.81, 162.80, 179.00. Anal. Calc. for $C_{31}H_{36}INO_4S$: C, 57.67; H, 5.62; N, 2.17. Found: C, 57.61; H, 5.54; N, 2.16%.

3.3.3. [5-Decyl-3-(2,4,6-trimethylphenyl)isoxazol-4-yl](phenyl)iodonium tosylate (3d)

Compound **3d**: 0.302 g (43%); m.p. 145–146 °C (CH_2Cl_2–hexane); ^{1}H-NMR ($CDCl_3$) δ 0.87–0.92 (m, 3H, Me), 1.10–1.27 (m, 14H, CH_2), 1.67 (s, 6H, Me), 1.76–1.83 (m, 2H, CH_2), 2.30 (s, 3H, Me), 2.35 (s, 3H, Me), 3.10–3.15 (m, 2H, CH_2), 6.85 (s, 2H, ArH), 6.97–7.15 (m, 4H, ArH), 7.25–7.47 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 14.08, 19.49, 21.20 (two signals overlapped), 22.63, 27.18, 27.39, 29.26, 29.28, 29.32, 29.47, 29.50, 31.84, 85.56, 116.43, 123.01, 125.69, 128.28, 128.47, 130.59, 131.13, 135.29, 137.81, 139.36, 139.97, 141.90, 162.89, 179.11. Anal. Calc. for $C_{35}H_{44}INO_4S$: C, 59.91; H, 6.32; N, 2.60. Found: C, 59.86; H, 6.31; N, 1.96%.

3.3.4. [5-tert-Butyl-3-(2,4,6-trimethylphenyl)isoxazol-4-yl](phenyl)iodonium tosylate (3e)

Compound **3e**: 0.517 g (83%); m.p. 211–213 °C (dec.) (CH_2Cl_2–hexane); ^{1}H-NMR ($CDCl_3$) δ 1.64 (s,

9H, Me), 1.67 (s, 6H, Me), 2.32 (s, 3H, Me), 2.36 (s, 3H, Me), 6.85 (s, 2H, ArH), 7.00–7.18 (m, 4H, ArH), 7.26–7.48 (m, 5H, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.61, 21.25 (two signals overlapped), 29.67, 35.57, 81.29, 116.93, 123.02, 125.83, 128.35, 128.58, 130.80, 131.40, 135.03, 138.10, 139.37, 140.22, 142.10, 164.30, 182.98. Anal. Calc. for $C_{29}H_{32}INO_4S$: C, 56.40; H, 5.22; N, 2.27. Found: C, 56.14; H, 5.23; N, 2.25%.

*3.3.5. (Phenyl)[5-phenyl-3-(2,4,6-trimethylphenyl)-isoxazol-4-yl]iodonium tosylate (**3f**)*

Compound **3f**: 0.458 g (72%); m.p. 170–173 °C (CH_2Cl_2–hexane) (lit. [4] 173–176 °C); ^{1}H-NMR ($CDCl_3$) δ 1.73 (s, 6H, Me), 2.30 (s, 3H, Me), 2.39 (s, 3H, Me), 6.89 (s, 2H, ArH), 6.95–7.61 (m, 12H, ArH), 8.13–8.16 (m, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 19.61, 21.18, 21.25, 84.76, 117.24, 122.77, 125.26, 125.77, 128.33, 128.54, 128.62, 129.28, 130.69, 131.22, 131.86, 134.83, 138.05, 139.36, 140.16, 141.72, 164.44, 173.29. Anal. Calc. for $C_{31}H_{28}INO_4S$: C, 58.40; H, 4.43; N, 2.20. Found: C, 58.30; H, 4.43; N, 2.13%.

*3.4. Reaction of isoxazolyliodonium triflate (**3a**) with Bu_4NF in the presence of trapping agents*

To a solution of [3-(2,4,6-trimethylphenyl)-5-(trimethylsilyl)isoxazol-4-yl](phenyl)iodonium triflate (**3a**) (1.0 mmol) and cyclopentadiene (5.0 mmol) in CH_2Cl_2 (15 ml) was added dropwise a THF solution of Bu_4NF (1.0 M, 1.2 ml) at 0 °C, and the reaction mixture was stirred at r.t. for 30 min. Water was added and then the resulting mixture was extracted with CH_2Cl_2. The organic extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using hexane–CH_2Cl_2 as the eluent. Evaporation of the solvent gave colorless crystals of 2,4,6-trimethylbenzonitrile (**5**) (0.125 g, 86%): m.p. 47–50 °C (lit. [12] 50–52 °C). IR (KBr) 2219.7 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, 3H, Me), 2.48 (s, 6H, Me), 6.93 (s, 2H, ArH); ^{13}C-NMR ($CDCl_3$) δ 20.5, 21.5, 110.5, 117.4, 128.2, 141.9, 142.8.

Acknowledgements

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