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GENERATION AND REACTIONS OF HETEROAROMATIC ARYNES USING HYPERVALENT IODINE COMPOUNDS

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Abstract – The heterocyclic aryne precursors, (phenyl)[1-phenyl-6-(trimethylsilyl)benzotriazol-5-yl]iodonium triflate and [3-ethoxycarbonyl-6-(trimethylsilyl)indazol-5-yl](phenyl)iodonium triflate, were prepared from the cycloadducts of 4,5-bis(trimethylsilyl)benzyne generated from (phenyl)[2,4,5-tris(trimethylsilyl)phenyl]iodonium triflate. These precursors provide the corresponding arynes, 1-phenyl-5,6-didehydrobenzotriazole and 3-ethoxycarbonyl-5,6-didehydroindazole, to give the corresponding polycyclic heteroaromatic compounds in good to high yields.

Heterocyclic aromatic compounds are important compounds which attract much attention as functional materials as well as materials of pharmaceutical and agricultural chemicals. Arynes are suitable reactive intermediates to construct annulated aromatic compounds using cycloaddition reactions.¹ In recent years, the applications of arynes to the synthesis of polycyclic aromatic compounds and the total synthesis of natural products were reviewd.² The significance of the aryne strategy is still noted in organic chemistry. However, arynes bearing a heterocyclic skeleton were little reviewed until now, in spite of having recognized the importance in chemistry. Very recently, it was reviewed about the use of heterocyclic arynes in organic synthesis, stating that mild conditions are required for the generation of heterocyclic arvnes.³ We have so far studied on hypervalent iodine benzyne precursors which can generate benzynes conditions⁴ under mild Verv recently, we developed an efficient synthesis of (phenyl)[2,4,5-tris(trimethylsilyl)phenyl]iodonium triflate (2) from 1,2,4,5-tetrakis(trimethylsilyl)benzene (1) using (diacetoxyiodo)benzene [PhI(OAc)₂], and found that this iodonium triflate 2 was utilized as an synthetic equivalent of 1,4-benzdiyne.⁵

Dedicated with respect to Prof. Dr. Isao Kuwajima on the occasion of his 77th birthday

Thus, as shown in Scheme 1, we expected that the 1,4-benzdiyne strategy was applicable to synthesis of heterocyclic aryne precursors using cycloaddition reactions of aryne **3** with phenylazide or ethyl diazoacetate. In order to confirm the aryne strategy described in Scheme 1, we conducted the synthesis of iodonium triflates having heterocyclic skeletons and the generation of the corresponding heterocyclic arynes. Here we want to report the synthesis and reactions of aryne precursors bearing triazole and indazole skeletons.



Scheme 1

At first, we examined the cycloaddition reaction of 4,5-bis(trimethylsilyl)benzyne (**3**) with phenylazide or ethyl diazoacetate using 2,4,5-tris(trimethylsilyl)phenyliodonium triflate **2**, as shown in Scheme 2. The preparation of iodonium triflate **2** was conducted according to our method reported recently.⁵ When iodonium triflate **2** was treated with a THF solution of Bu₄NF in the presence of phenylazide in CH₂Cl₂ at 0 °C, the cycloadduct **4** was obtained in 76% yield. Similarly, the reaction of iodonium triflate **2** with Bu₄NF in the presence of ethyl diazoacetate gave the cycloadduct **5** in 94% yield. These results indicate that 4,5-bis(trimethylsilyl)benzyne (**3**) was generated under mild conditions and efficiently trapped with phenylazide or ethyl diazoacetate. The cycloaddition proceeded without any damage of two trimethylsilyl groups. Then, the disilyl cycloadducts thus obtained were converted to the corresponding aryne precursors.



The conversion of 1-phenyl-5,6-bis(trimethylsilyl)benzotriazole (4) to a didehydrobenzotriazole precursor was conducted using a hypervalent iodine reagent. The results are given in Table 1. The reaction was performed as follows. First, iodosylbenzene was treated with $BF_3 \cdot OEt_2$ in CH_2Cl_2 to activate it and then reacted with bis(trimethylsilyl)benzotriazole 4. Although the reaction mixture was treated with aqueous NaOTf to convert to the triflate salt, no desired product was obtained (Entry 1). Next, the similar reaction was conducted in 1,2-dichloroethane at 40 °C. The desired iodonium triflate 6 was obtained in 8% yield (Entry 2), but elevation of the reaction temperature did not improve the result (Entries 3 and 4). When the solvent was replaced by acetonitrile, the yield of iodonium triflate 6 increased (Entry 5) to 51%. However, the reaction with PhI(OAc)₂ instead of PhIO resulted in lowering the yield (Entry 6).

Ph N N N	SiMe ₃ SiMe ₃	1. PhIO/BF ₃ ∙(2. aq. NaOTf	⊃Et ₂	Ph N N N I(F	Me ₃ Ph)OTf			
Entry	Substrate (mmol)	PhIO (mmol)	BF ₃ ·OEt ₂ (mmol)	Solvent (mL)	Time (h)	Temp (°C)	Yield $(\%)^a$	
1	0.5	0.6	3.0	DCM (4)	2	0	0	
2	0.2	0.24	1.2	DCE (2)	5	40	8	
3	0.2	0.24	1.2	DCE (2)	5	60	4	
4	0.2	0.24	1.2	DCE (2)	5	80	6	
5	2.0	2.4	12	MeCN (20)	4	40	51	
6	0.5	0.6^{b}	1.2	MeCN (2)	4	40	15	

Table 1. Synthesis of a Didehydrobenzotriazole Precursor

^a Isolated yield. ^b PhI(OAc)₂ was used instead of PhIO.

Generation of an aryne from iodonium triflate 6 was conducted by the reaction of 6 with Bu₄NF. When iodonium trifalte 6 was treated with 1.2 equivalents of Bu₄NF in the presence of furan (5 equivalents) in CH₂Cl₂ at 0 °C, the cycloadduct 8 with furan was obtained in 95% isolated yield. In the case of tetraphenylcyclopentadienone as a trapping agent, the reaction of 6 with Bu₄NF gave the cycloadduct 9 in 93% which the cycloaddition of aryne 7 isolated vield. was derived from with teteraphenylcyclopentadienone followed by decarbonylation. In addition, the reaction of 6 with Bu₄NF in the presence of anthracene gave the cycloadduct 10 derived from the cycloaddition of 7 with anthracene, in 79% yield.



Scheme 3

In analogy with the synthesis of didehydrobenzotriazole precursor **6**, the reaction of disilyl-substituted indazole **5** was conducted using PhIO activated with $BF_3 \cdot OEt_2$ in MeCN and followed by treating with aqueous NaOTf. The desired iodonium triflate **11** was obtained in 91% yield (Table 2, Entry 1). Moreover, the reaction with PhI(OAc)₂ activated with $BF_3 \cdot OEt_2$ also gave the iodonium triflate **11** in 72% yield (Entry 2).

 Table 2. Synthesis of a Didehydroindazole Precursor

EtO ₂ C	SiMe ₃	1. PhIO/BF ₃ ·OEt ₂		EtO ₂ C	∠l(Ph)OTf		
N N H SiMe ₃		2. aq. NaOTf		N H H 11	∑SiMe₃		
Entry	5 (mmol)	PhIO (mmol)	BF₃·OEt₂ (mmol)	Solvent (mL)	Time (h)	Temp (°C)	Yield $(\%)^a$
1	1	1.2	6	MeCN (10)	1	40	91
2	0.5	0.6^{b}	1.2	$CH_2Cl_2(5)$	0.5	rt	72

^a Isolated yield. ^b PhI(OAc)₂ was used instead of PhIO.

When the iodonium triflate 11 was treated with Bu_4NF in the presence of furan in CH_2Cl_2 at 0 °C, the cycloadduct 13 with furan was obtained in 94% isolated yield. This reaction indicates that 3-ethoxycarbonyl-5,6-didehydroindazole (12) is generated almost quantitatively under the present reaction conditions. The trapping reaction with tetraphenylcyclopentadienone gave the cycloadduct 14 with 12 in 97% isolated yield. In the case of anthracene as a trapping reagent, tripticene derivative 15 was obtained in 52% isolated yield.



In summary, we have demonstrated that two new heterocyclic arynes, 1-phenyl-5,6-didehydrobenzotriazole (7) and 3-ethoxycarbonyl-5,6-didehydroindazole (12), can be generated efficiently from the corresponding iodonium triflates 6 and 11. The cycloaddition of the heterocyclic arynes 7 and 12 with furan, tetraphenylcyclopentadienone, or anthracene provides the corresponding annulated heterocyclic compounds in good to high yields. These results suggest that the heterocyclic aryne strategy is useful to construct the polycyclic heteroaromatic compounds.

EXPERIMENTAL

All solvents and starting materials were used during the research work as received without further purification unless otherwise indicated. ¹H and ¹³C NMR were recorded on a Agilent 400-MR NMR

spectrometer (TMS as an internal standard). Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. High resolution mass spectra were measured by the Analytical Center, Institute for Materials Chemistry and Engineering, Kyushu University. Column chromatographic separation was carried out using Silica Gel 60, spherical (Kanto Chemical Co.). Pre-coated plates (silica gel 60 F₂₅₄, MERCK) were used for TLC examination.

Preparation of 1-Phenyl-5,6-bis(trimethylsilyl)benzotriazole (4)

To a solution of (phenyl)[tris(trimethylsilyl)phenyl]iodonium triflate (**2**) (1 mmol) and phenylazide (5 mmol) in CH₂Cl₂ (5 mL) was added a THF solution of Bu₄NF (1 mmol) at 0 °C and stirred for 20 min at this temperature. The reaction mixture was poured into water and extracted with CH₂Cl₂ (10 mL × 3). The combined organic extract was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The product was separated by column chromatography on silica gel (hexane/AcOEt) to give 1-phenyl-5,6-bis(trimethylsilyl)benzotriazole (**4**) (0.258 g, 76%) as white crystals. Mp 116-117 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.44 (s, 9H), 0.46 (s, 9H), 7.52 (t, *J* = 8 Hz, 1H), 7.64 (t, *J* = 8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H), 8.10 (s, 1H), 8.51 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 2.0, 2.1, 117.2, 122.6, 127.5, 128.5, 129.9, 131.7, 137.0, 141.4, 146.2, 146.5. HRMS (EI) calcd for C₁₈H₂₅N₃Si₂ (M⁺): 339.1587; found: 339.1589.

Preparation of 3-Ethoxycarbonyl-5,6-bis(trimethylsilyl)indazole (5)

The similar reaction of **2** (2 mmol) and ethyl diazoacetate (10 mmol) in CH₂Cl₂ (10 mL) was carried out using a THF solution of Bu₄NF (2 mmol). Workup of the reaction mixture gave 3-ethoxycarbonyl-5,6-bis(trimethylsilyl)indazole (**5**) (0.628 g, 94%) as white crystals. Mp 198-200 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.456 (s, 9H), 0.459 (s, 9H), 1.53 (t, *J* = 7 Hz, 2H), 4.58 (q, *J* = 7 Hz, 3H), 8.30 (d, *J* = 7 Hz, 1H), 8.60 (s, 1H), 12.9 (s, 1H); ¹³C NMR (100 MHz, DMSO) δ 2.1, 2.2, 14.4, 61.0, 119.8, 121.4, 129.0, 136.0, 139.0, 141.4, 144.3, 163.4. HRMS (EI) calcd for C₁₆H₂₆N₂O₂Si₂ (M⁺): 334.1533; found: 334.1533.

Preparation of (Phenyl)[1-phenyl-6-(trimethylsilyl)benzotriazol-5-yl]iodonium Triflate (6)

To a mixture of benzotriazole 4 (2 mmol) and PhIO (2.4 mmol) in MeCN (20 mL) was added BF₃·OEt₂ (12 mmol) and the mixture was stirred at 40 °C for 4 h. The reaction mixture was poured into an aqueous solution of NaOTf (20 mmol) and stirred vigorously. The product was extracted with CH_2Cl_2 (20 mL \times 3). The combined organic extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The and resulting solid filtered washed with hexane to was give (phenyl)[1-phenyl-6-(trimethylsilyl)benzotriazol-5-yl]iodonium triflate (6) (0.315 g, 51%) as yellow crystals. Mp 91-104 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.50 (s, 9H), 7.46-7.89 (m, 10H), 8.04 (s, 1H), 9.01 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 0.3, 114.6, 114.7, 120.1, 123.2, 129.7, 130.2, 132.1, 132.3,

133.0, 133.2, 133.7, 135.8, 145.2, 147.9. HRMS (FAB) calcd for $C_{21}H_{21}IN_3Si$ (M⁺–OTf): 470.0544; found 470.0549.

Trapping Reactions of a 5,6-Didehydrobenzotriazole (7)

To a solution of iodonium triflate **6** (0.2 mmol) and a dienophile (1 mmol) in CH_2Cl_2 (1 mL) was slowly added a THF solution of Bu_4NF (0.24 mmol). The mixture was stirred at 0 °C for 20 min. The reaction mixture was poured into water and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The product was separated by column chromatography on silica gel (hexane/AcOEt).

5,9-Epoxy-5,9-dihydro-1-phenyl-1*H*-naphtho[2,3-*d*]triazole (8)

The product was obtained as white crystals, mp 119-121 °C; yield 0.050 g (95%); ¹H NMR (400 MHz, CDCl₃) δ 5.77 (s, 1H), 5.85 (s, 1H), 7.00 (d, *J* = 3 Hz, 1H), 7.07 (d, *J* = 3 Hz, 1H), 7.52-7.54 (m, 2H), 7.61 (t, *J* = 8 Hz, 2H), 7.72 (d, *J* = 8 Hz, 2H), 7.84 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 81.8, 81.9, 103.0, 111.3, 123.2, 128.9, 129.8, 131.4, 136.8, 141.6, 142.9, 144.7, 145.0, 149.2. HRMS (EI) calcd for C₁₆H₁₁N₃O (M⁺): 261.0902; found: 261.0907.

1,5,6,7,8-Pentaphenyl-1*H*-naphtho[2,3-*d*]triazole (9)

The product was obtained as yellow crystals, mp 232-233 °C; yield 0.102 g (93%). The spectra were in accord with the reported ones.^{5b}

5,10[1',2']-Benzeno-1-phenyl-1*H*-anthra[2,3-*d*]triazole (10)

The product was obtained as yellow crystals, mp 197-199 °C; yield 0.059 g (79%). The spectra were in accord with the reported ones.^{5b}

Preparation of [3-Ethoxycarbonyl-6-(trimethylsilyl)indazol-5-yl](phenyl)iodonium Triflate (11)

To a mixture of indazole 5 (1 mmol) and PhIO (1.2 mmol) in MeCN (10 mL) was added BF₃·OEt₂ (6 mmol) and the mixture was stirred at 40 °C for 1 h. The reaction mixture was poured into an aqueous solution of NaOTf (10 mmol) and stirred vigorously. The product was extracted with CH_2Cl_2 (10 mL \times 3). The combined organic extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting solid filtered washed with was and hexane to give [3-ethoxycarbonyl-6-(trimethylsilyl)indazol-5-yl](phenyl)iodonium triflate (11) (0.559 g, 91%) as white crystals. Mp 218-220 °C; ¹H NMR (400 MHz, CD₃CN) δ 0.43 (s, 9H), 1.42 (t, J = 7 Hz, 3H), 4.47 (q, J = 7 Hz, 2H), 7.50 (t, J = 8 Hz, 2H), 7.64 (t, J = 8 Hz, 1H), 7.79 (d, J = 8 Hz, 2H), 8.10 (s, 1H), 9.12 (s, 1H), 12.4 (s. 1H); ¹³C NMR (100 MHz, CD₃CN) δ 0.6, 14.9, 62.6, 114.4, 115.1, 123.6, 126.2, 133.6, 133.7, 134.1, 136.1, 138.3, 143.0, 143.9, 162.9. HRMS (FAB) calcd for $C_{19}H_{22}IN_2O_2Si$ (M⁺–OTf): 465.0495; found: 465.0495.

Trapping Reactions of a Didehydroindazole (12)

To a solution of iodonium triflate **11** (0.2 mmol) and a dienophile (1 mmol) in CH_2Cl_2 (1 mL) was slowly added a THF solution of Bu_4NF (0.24 mmol). The mixture was stirred at 0 °C for 20 min. The reaction mixture was poured into water and extracted with CH_2Cl_2 (10 mL × 3). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The product was separated by column chromatography on silica gel (hexane/AcOEt). In the trapping reaction with anthracene, iodonium triflate **11** (0.1 mmol) was used.

Ethyl 5,8-Epoxy-5,8-dihydro-1*H*-benzo[*f*]indazole-3-carboxylate (13)

The product was obtained as white crystals, mp 173-174 °C; yield 0.048 g (94%); ¹H NMR (400 MHz, CDCl₃) δ 1.47 (t, *J* = 7 Hz, 3H), 4.54 (q, *J* = 7 Hz, 2H), 5.77 (s, 1H), 5.80 (s, 1H), 6.97-7.04 (m, 2H), 7.58 (s, 1H), 7.92 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 61.1, 81.88, 81.91, 104.4, 112.5, 120.2, 140.5, 141.6, 142.6, 143.0, 147.8, 163.0 (one carbon overlapped). HRMS (EI) calcd for C₁₄H₁₂N₂O₃ (M⁺): 256.0848; found: 256.0850.

Ethyl 5,6,7,8-Tetraphenyl-1*H*-benzo[*f*]indazole-3-carboxylate (14)

The product was obtained as white crystals, mp 330-332 °C; yield 0.106 g (97%); ¹H NMR (400 MHz, CDCl₃) δ 1.27 (t, *J* = 7 Hz, 3H), 4.39 (q, *J* = 7 Hz, 2H), 6.88 (m, 10H), 7.24-7.28 (m, 10H), 7.76 (s, 1H), 8.57 (s, 1H), 10.4 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.9, 61.1, 106.0, 120.7, 122.2, 125.36, 125.41, 126.6, 127.6, 127.7, 129.7, 131.1, 131.3, 131.4, 132.3, 137.1, 137.5, 137.7, 139.3, 139.5, 139.6, 139.8, 140.4, 162,6 (5 carbons overlapped). HRMS (FAB) calcd for C₃₈H₂₈N₂O₂ (M⁺): 544.2151; found: 544.2149.

Ethyl 5,10[1',2']-Benzeno-1*H*-naphtho[2,3-*f*]indazole-3-carboxylate (15)

The product was obtained as yellow crystals, mp 195-197 °C; yield 0.038 g (52%); ¹H NMR (400 MHz, CDCl₃) δ 1.46 (t, *J* = 7 Hz, 3H), 4.51 (q, *J* = 7 Hz, 2H), 5.47 (s, 1H), 5.53 (s, 1H), 7.00-7.02 (m, 4H), 7.38-7.43 (m, 4H), 7.58 (s, 1H), 8.12 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 53.8, 54.2, 61.0, 105.9, 115.8, 120.3, 123.7, 123.7, 125.5, 125.7, 136.2, 139.8, 140.7, 144.2, 144.8, 144.9, 162.9. HRMS (EI) calcd for C₂₄H₁₈N₂O₂ (M⁺): 366.1368; found: 366.1366.

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