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Novel Formation of Iodobenzene Derivatives from 1-(Methylthio)-3-tosylhexa-1,3-dien-5-ynes via Iodine-Induced Intramolecular Cyclization

Shoji Matsumoto, Kenji Takase, and Katsuyuki Ogura*

Department of Applied Chemistry and Biotechnology, Graduate School of Engineering, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263-8522, Japan

katsuyuki@faculty.chiba-u.jp

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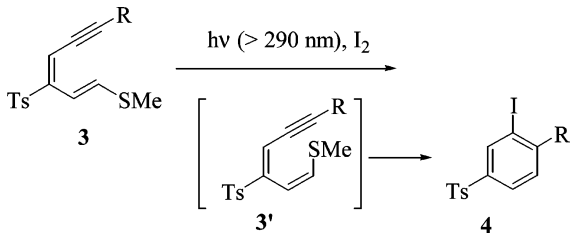
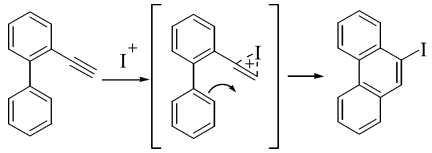


The reaction of (1*E*,3*E*)-1-(methylthio)-3-tosylhexa-1,3-dien-5-ynes (**3**) with iodine to form iodine-substituted benzenes (**4**) is reported. The reaction of **3** with iodine proceeded very slowly, but UV irradiation accelerates the reaction to give **4** in high-to-excellent yields. Irradiation induces the *cis-trans* isomerization of the C1−C2 double bond, leading to the (1*Z*,3*E*)-geometric isomer (**3′**), which easily reacts with iodine to afford **4**. This reaction is applicable to 3-(methoxycarbonyl)-1-(methylthio)-6-phenylhexa-1,3-dien-5-yne (**11**), which is synthesized as a geometric mixture. Interestingly, this mixture can be used as the starting material. Irradiation of the mixture (the geometric isomer ratio = 50:28:5:17) with iodine resulted in the formation of methyl 3-iodo-4-phenylbenzoate (**12**) in 80% yield.

Introduction

Haloarenes constitute an important class of molecules in synthetic organic chemistry. Especially, iodoarenes form a carbon−carbon bond via a catalytic cross-coupling reaction[1] so efficiently that they are used as potential intermediates for synthesizing naturally occurring products, biologically active compounds, and functional materials.[2] Various reactions leading to iodoarenes have been reported: (1) direct iodination of aromatic precursors,[3] (2) light-induced cyclization of 1-aryl-1-alken-3-ynes in the presence of iodine,[4] (3) catalytic cyclizations of iodinated polyenyne derivatives,[5−7] and (4) 6-endo-dig electrophilic cyclization of alkyne derivatives (eq 1).[8]



(1)

We were interested in the fourth reaction (eq 1) from the viewpoint that an iodonium intermediate reacts intramolecularly

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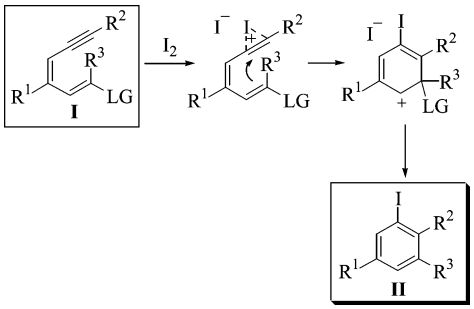
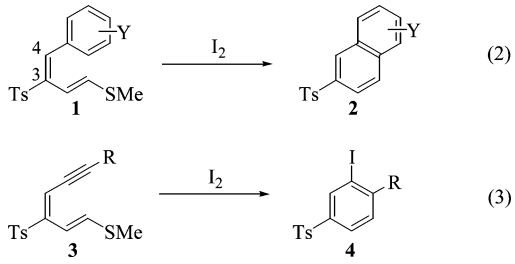
SCHEME 1. Strategy for Iodobenzene Formation



with a benzene ring as a nucleophile to give various iodinated polyarenes. The iodonium intermediate is formed by the attack of iodonium ion on the triple bond. We would obtain iodobenzene derivatives (**II**) that have substituent(s) at the optional position(s) if this reaction were extended to a 1,3-alkadien-5-yne system (**I**). To achieve the expected reaction, a few problems must be overcome: the first is how to synthesize the starting **I**. In addition, it is important to force **I** to adopt the conformation around the C−C single bond that is suitable for cyclization (Scheme 1).

Recently, we reported the cyclization reaction of 4-aryl-1-(methylthio)-3-tosylbuta-1,3-dienes (**1**) with iodine to give the corresponding naphthalenes (**2**) (eq 2).[9] In this cyclization, the methylthio group acts as a leaving group and the tosyl group compels the geometry of the C3−C4 double bond to be *E*.[9,10] Herein, we wish to report the first example for the iodine-induced cyclization of 1-(methylthio)-3-tosylhexa-1,3-dien-5-ynes (**3**) and its related compounds (eq 3).



Results and Discussion

First, we investigated the iodine-induced reaction of 6-phenyl-1-(methylthio)-3-tosylhexa-1,3-dien-5-yne (**3a**), which was prepared by a procedure similar to the synthesis of **1**:[9] the condensation of (*E*)-1-(methylthio)-3-tosylpropene (**5**) with 3-phenylpropynal (**6**), as shown in Scheme 2. After the lithiated **5** was added to **6**, acetylation with acetic anhydride and the subsequent treatment with triethylamine gave **3a**. In this reaction

SCHEME 2. Preparation of Dienyne Compound 3a

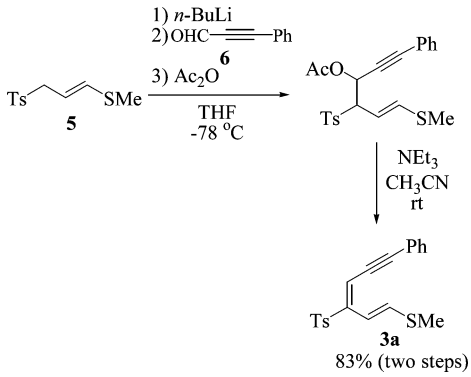
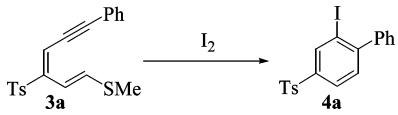
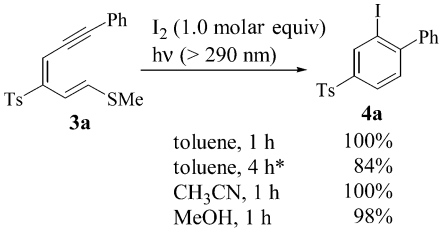


TABLE 1. Iodobenzene Ring Formation of 3a with Iodine under Thermal Conditions



entry	molar equiv of I_2	solvent	conditions	yield (%)
1	0.5	CH_3CN	rt, 17 h	trace
2	0.5	CH_3CN	40 °C, 6 days → reflux, 3 days	6
3	1.0	CH_3CN	40 °C, 22 h	trace
4	1.0	$CHCl_3$	rt, 2 days → reflux, 4 days	33
5	1.0	toluene	80 °C, 5 days	53

SCHEME 3. Reaction of 3a with Iodine under UV Irradiation



sequence, **3a** was obtained as a single geometric isomer. Using the analogy of the previous results, the geometry of **3a** was assigned as *E,E*.[9,10]

The thus-obtained **3a** was subjected to reaction with iodine. The expected reaction to form 2-iodo-4-tosyl-1,1′-biphenyl (**4a**) took place at an elevated temperature (40−80 °C). The yield of **4a** was low in all cases examined (Table 1). The best yield of 53% was attained using the reaction in toluene at 80 °C for 5 days (entry 5). The spectroscopic data (^{1}H NMR and IR) and elemental analysis were consistent with the structure of **4a**. Finally, the structure **4a** was confirmed by single-crystal X-ray crystallography.

It is noteworthy that the reaction of **3a** under thermal conditions required a long period of reaction time. This is probably true because **3a** mainly adopts the conformation that disfavors the cyclization. Next, we irradiated the solution of **3a** and iodine in expectation either that the excitation of **3a** would assist the cyclization reaction or that isomerization of the olefinic linkage(s) would occur photochemically to form the geometric isomer suitable to the cyclization. To our delight, **4a** was formed quantitatively when a solution of **3a** and iodine (1.0 molar equiv)

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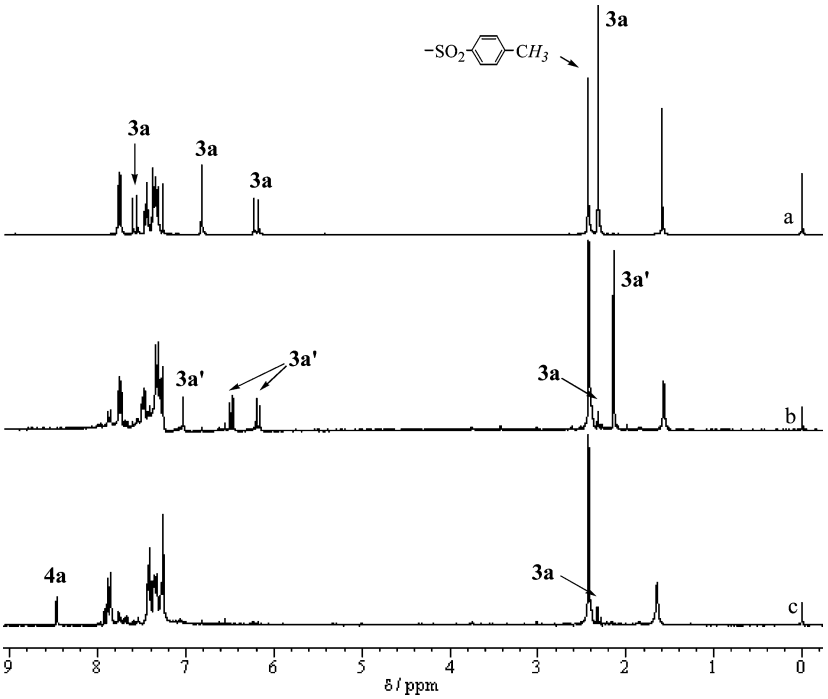
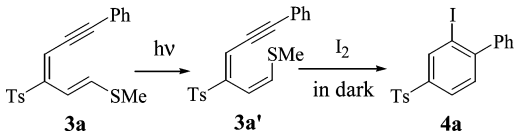
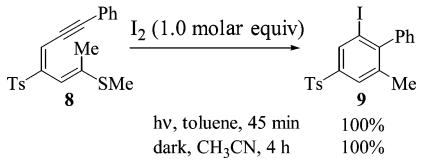


FIGURE 1. ^{1}H NMR analysis of the reaction of **3a** in $CDCl_3$: (a) before and (b) after the external irradiation for 15 min with a high-pressure mercury lamp through a Pyrex filter. (c) Addition of I_2 (1 molar equiv) into spectrum b in the dark (after 5 min).

SCHEME 4. Reaction Sequence of the Formation of 4a



SCHEME 5. Reaction of 8 with Iodine



in toluene was irradiated using a high-pressure mercury lamp through a Pyrex filter (Scheme 3). The reaction was tolerant of the polarity of the employed solvent. The smooth reaction occurred not only in nonpolar toluene but also in polar CH_3CN and MeOH. Interestingly, **4a** was obtained in 84% yield on irradiation using 0.5 molar equiv of iodine, although a prolonged reaction time was required.

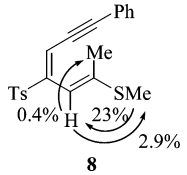
The methylthio group of **3a** plays an important role in the present reaction because 1-chloro-6-phenyl-3-tosylhexa-1,3-dien-5-yne (**7**), which has a chlorine atom instead of the methylthio group, gave **4a** in 26% yield under similar conditions (irradiation in toluene for 5 h).

To gain insight into the role of irradiation in this system, the reaction was followed using ^{1}H NMR. The results are summarized in Figure 1. When a solution of **3a** in $CDCl_3$ was externally irradiated with a high-pressure arc lamp, a new set of proton signals [δ 6.18 (d, 1H, J = 10.6 Hz), 6.49 (d, 1H, J = 10.6 Hz), and 7.04 (s, 1H)] (Figure 1b) appeared instead of those [δ 6.24 (d, 1H, J = 15.6 Hz), 6.82 (s, 1H), and 7.58 (d, 1H, J = 15.6 Hz)] of **3a** (Figure 1a). Upon treatment of the resulting solution with iodine in the dark, **4a** was formed immediately at room temperature (Figure 1c). In an alternative run, the new product was isolated and the geometry of its C1−C2 double bond was assigned from the coupling constant (10.6 Hz) between H1 and H2 to be *Z*. Consequently, the irradiation was shown to hasten the transformation of **3a** to **4a** via the 1*Z*-isomer (**3a′**), which easily cyclizes with iodine (Scheme 4).

These facts seem to imply that the substituent at the 1*Z* position of 1-(methylthio)-3-tosylhexa-1,3-dien-5-yne system accelerates the cyclization reaction with iodine. Consequently, we also synthesized 1-methyl-1-(methylthio)-6-phenyl-3-tosylhexa-1,3-dien-5-yne (**8**),[11] which was subjected to the reaction with iodine (Scheme 5). As anticipated, the desired tetrasubstituted benzene derivative, 2-iodo-6-methyl-4-tosyl-1,1′-biphenyl (**9**), was obtained in almost quantitative yield on irradiation in toluene containing iodine (1.0 molar equiv). The reaction of **8** with iodine in CH_3CN proceeded smoothly at room temperature in the dark, and the biphenyl (**9**) was formed quantitatively after 4 h.

Next, we would like to describe the reaction mechanism for leading from the starting **3** to the final **4**. The UV irradiation brings about the *cis-trans* isomerization of the C1−C2 double bond of **3** to form the (1*Z*,3*E*)-geometric isomer (**3′**). The intermediary **3′** was shown to easily react with iodine and afford **4** in a high yield (Figure 1). Hitherto, the iodine-induced cyclization of conjugated diene-yne systems has been reported to be initiated by the attack of an iodonium ion[8] or an iodine atom (radical).[4] Since the iodine molecule splits into iodine

(11) The geometry of the C−C double bond at the 1,2-position in **8** was determined using NOE measurements.



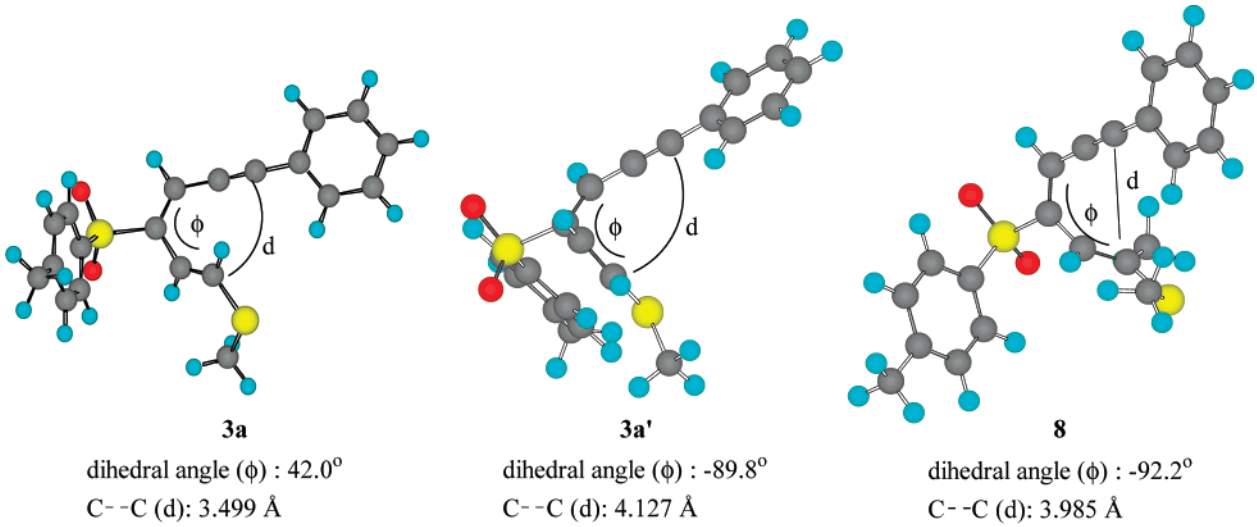
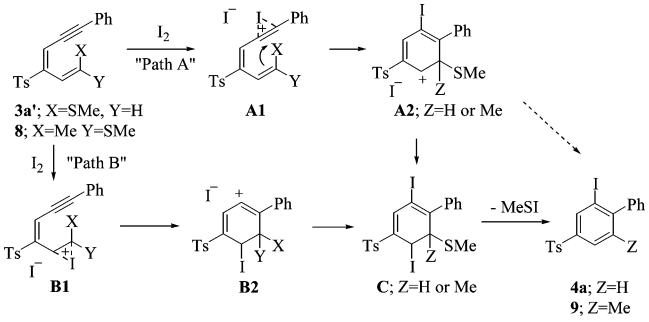


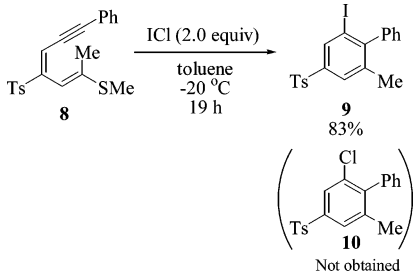
FIGURE 2. The most stable conformations of **3a**, **3a′**, and **8** calculated using the PM3 theory.

SCHEME 6. Plausible Reaction Mechanisms



atoms (radicals) photochemically, we cannot eliminate the possibility that the reaction of **3′** with iodine under the UV irradiation involves an iodine radical. Here, the mechanism for the reaction of **3a′** with iodine in the dark is discussed. In Scheme 3, the reaction was shown to occur efficiently in toluene, CH_3CN, and MeOH. This does not suggest that the reactions of the *Z*-isomer (**3a′**) with iodine in these solvents take place at the same rate. We compared the reaction rate in benzene-d_6 with that in acetonitrile-d_3. In an NMR tube, the compound (**3a**) was externally irradiated in benzene-d_6 or acetonitrile-d_3 to obtain **3a′** mainly, and then, after addition of iodine, the reaction in the dark was pursued by ^{1}H NMR (see the Supporting Information). The reaction of **3a′** with iodine in acetonitrile-d_3 was much faster than that in benzene-d_6. In the reaction in acetonitrile-d_3, the starting **3a′** disappeared completely within 4 min. In contrast, 24 and 5% of the starting **3a′** remained unchanged after 4.5 and 10 min, respectively, in benzene-d_6. This result supports the idea that the reaction of **3a′** in the dark proceeds via an ionic mechanism. Possibly, the iodonium ion attacks either on the triple bond (Path A)[8,12−15] or on the terminal double bond (Path B),[9a] as depicted in Scheme 6. After the

SCHEME 7. Reaction of 8 with Iodine Monochloride



iodonium ion is bound to the triple bond or the terminal double bond, intramolecular cyclization takes place to form a cationic intermediate (**A2** or **B2**), which reacts with the iodide ion. The subsequent aromatization through the removal of methanesulfenyl iodide forms **4** or **9**. At present, we cannot eliminate the possibility that the aromatization of the intermediary **A2** is directly achieved by the attack of an iodide ion on its sulfur atom. Because methanesulfenyl iodide is so unstable that it is converted immediately to dimethyl disulfide and iodine, one-half of the iodine used at the initial stage is reproduced.[16] For that reason, a high yield was attained even with 0.5 molar equiv of iodine (Scheme 3).

We examined the reaction of **8** with iodine monochloride, which releases iodonium ion and chloride ion smoothly, to clarify the attacking position of the iodonium ion. The intermediate (**B2**; X = Me, Y = SMe) would react with a chloride ion to form 2-chloro-6-methyl-4-tosyl-1,1′-biphenyl (**10**) if the reaction proceeds through Path B. In contrast, the reaction via Path A would form compound **9**. The fact is that **9** was formed in the reaction of **8** with iodine monochloride (Scheme 7), which supports Path A for the reaction of **3** and **8** with iodine.

At present, the reason why the 1*Z*-isomer (**3a′**) of **3a** reacts with iodine much more rapidly than **3a** (1*E*-isomer) remains

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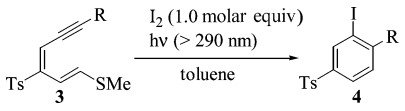
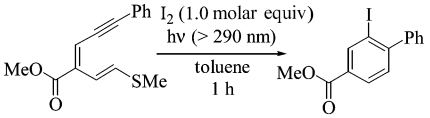
TABLE 2. Iodobenzene Ring Formation of 3 with Iodine under Photoirradiation[a]



entry	R	time (h)	yield (%) of **4**
1	*p*-MeOC$_6$H$_4$ (**3b**)	1	100
2	*p*-BrC$_6$H$_4$ (**3c**)	1	83[b]
3	*p*-MeOC(O)C$_6$H$_4$ (**3d**)	1.5	86[c]
4	*n*-C$_{12}$H$_{25}$ (**3e**)	1	91

[a] Reaction conditions: **3** and I_2 (1.0 molar equiv) in toluene (0.01 M) under a high-pressure Hg lamp. [b] Starting material was recovered in 17% yield. [c] Starting material was recovered in 10% yield.

SCHEME 8. Reaction of Compound (*E*,*E*)-11 Having a Methoxycarbonyl Group with Iodine



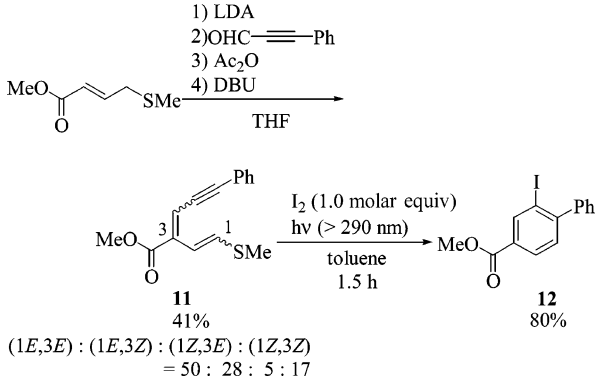
questionable. Although the complete answer remains elusive, some comments are presented. As described in the Introduction, it is likely that, if the molecule adopts a conformation suitable to the cyclization, it would react with iodine smoothly. For that reason, we calculated the most stable conformations (Figure 2) of **3a**, **3a′**, and **8** with the PM3 theory of MOPAC.[17] Apparently, the distance (*d*) between the carbons that are bound in the reaction does not seem to be related to the reactivity because the less reactive **3a** has the shortest distance. We noticed that the dihedral angle between the adjacent double bonds of the reactive **3a′** and **8** is approximately 90°, whereas that of the less reactive **3a** is 42°, which suggests that the reactive compound (**3a′** or **8**) has the p orbital of the terminal double bond facing the triple bond. Therefore, it is reasonably rationalized that, in the reaction of **3a′** or **8**, the triple bond reacts smoothly with the terminal double bond after it undergoes the attack of the iodonium ion.

Furthermore, we prepared various 6-substituted 1-(methylthio)-3-tosylhexa-1,3-dien-5-ynes (**3**) according to procedures similar to that shown in Scheme 2 and examined the reaction with iodine. As portrayed in Table 2, the corresponding 1-substituted 2-iodo-4-tosylbenzenes (**4**) were formed in high-to-excellent yields on the irradiation in the presence of iodine. It should be noted that a 6-dodecyl derivative (**3e**) was also transformed into the corresponding **4e** in 91% yield.

Finally, we present an example implying that the reaction of **3** with iodine is widely applicable. The corresponding methyl 4-phenyl-3-iodobenzoate (**12**) was isolated in 75% yield when the compound (*E*,*E*)-**11**, having a methoxycarbonyl group instead of a tosyl group, was subjected to the reaction with iodine under irradiation (Scheme 8).

The starting compound (**11**) was synthesized from methyl γ-(methylthio)crotonate using a method similar to the preparation of **3**. Using this method, the 1,3-alkadien-5-yne system was formed as a geometric mixture, which was separated by chromatography to yield **11**. As described above, the irradiation

SCHEME 9. Formation of 12 from a Geometric Mixture of 11



brings about geometric isomerization around the C−C double bonds, suggesting that the geometric mixture of **11** is suitably used as the starting material. Indeed, the reaction of a geometric mixture (*E*,*E*:*E*,*Z*:*Z*,*E*:*Z*,*Z* = 50:28:5:17) of **11** gave **12** in 80% yield (as determined by NMR analysis) (Scheme 9).

In conclusion, results of this study demonstrated the efficient formation of iodobenzene derivatives (**4**) using iodonium-induced cyclization of 1-(methylthio)-3-tosylhexa-1,3-dien-5-ynes (**3**). In this reaction, UV irradiation accelerates the reaction to form **4** in high-to-excellent yields. The irradiation causes the *cis-trans* isomerization of the C−C double bond of **3** to produce the corresponding (1*Z*)-geometric isomer, which easily reacts with iodine to form **4**. The present reaction system is applicable to 3-(methoxycarbonyl)-1-(methylthio)-6-phenylhexa-1,3-dien-5-yne (**11**). In this case, a geometric mixture of **11** is used as a starting material. Because the irradiation of the geometric isomers in the presence of iodine gives the corresponding iodobenzene derivative (**12**) in a high yield, the present reaction is regarded as an efficient procedure for synthesizing the iodinated arenes.

Experimental Section

General Procedure for Preparation of (1*E*,3*E*)-1-(Methylthio)-3-tosylhexa-1,3-dien-5-ynes. (1*E*,3*E*)-1-(Methylthio)-6-phenyl-3-tosylhexa-1,3-dien-5-yne (3a): To a solution of (*E*)-1-(methylthio)-3-tosyl-1-propene (**5**)[18] (1.939 g, 8.00 mmol) in THF (50 mL) was added *n*-butyllithium (1.54 M in hexane; 5.5 mL, 8.5 mmol), and the resulting mixture was stirred for 10 min at −78 °C. 3-Phenylpropynal (**6**) (1.10 mL, 8.99 mmol) was added to the mixture at the same temperature, and the reaction mixture was stirred for 2 h. Then, acetic anhydride (0.84 mL, 8.9 mmol) was added at that temperature, and the mixture was additionally stirred for 1 h. The usual workup (quenching with saturated NH_4Cl solution, extraction with Et_2O, and evaporation) gave yellow oil (3.678 g). To a solution of that oil in undistilled CH_3CN (20 mL) was added triethylamine (1.65 mL, 11.8 mmol) at room temperature in air. The reaction was monitored by using TLC, and the resulting mixture was stirred for 5 h. The reaction mixture was evaporated and was subjected to column chromatography on SiO_2 (hexane/ethyl acetate = 3:1) to give **3a** (2.349 g, 6.63 mmol) in 83% yield as yellow solid. To use for the reaction, it was furthermore purified by recrystallization from hexane to give yellow plate crystals: mp 112.5−113.2 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.43 (s, 3H), 6.24 (d, 1H, *J* = 15.6 Hz), 6.82 (s, 1H), 7.29 (d, 2H, *J* = 8.5 Hz), 7.35−7.39 (m, 3H), 7.45 (diffused d, 2H, *J* = 7.8 Hz),

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7.58 (d, 1H, J = 15.6 Hz), 7.76 (d, 2H, J = 8.4 Hz); IR (KBr) 3059, 2920, 2185, 1595, 1576, 1319, 1157, 1122, 723, 660, 600 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_2S_2$: C, 67.76; H, 5.12. Found: C, 67.73; H, 5.14.

The Reaction of 3a with Iodine under Thermal Conditions: To a solution of **3a** (0.177 g, 0.50 mmol) in toluene (12.5 mL) was added iodine (0.127 g, 0.50 mmol), and the resulting mixture was refluxed for 5 days. To the reaction mixture was added ethyl acetate (10 mL) and washed with saturated $Na_2S_2O_3$ solution (10 mL × 4). The organic layer was dried with $MgSO_4$, evaporated, and subjected to column chromatography on SiO_2 (chloroform/hexane = 6:1) to give 2-iodo-4-tosyl-1,1′-biphenyl (**4a**) (0.115 g, 0.265 mmol) in 53% yield as white solid. **4a** was further purified by recrystallization from hexane and chloroform to obtain as colorless plate crystals: mp 128.1−128.7 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 7.27 (m, 2H), 7.35 (d, 2H, J = 8.5 Hz), 7.39 (d, 1H, J = 8.1 Hz), 7.42−7.44 (m, 3H), 7.87 (d, 2H, J = 8.4 Hz), 7.92 (dd, 1H, J = 1.9 and 8.0 Hz), 8.47 (d, 1H, J = 1.9 Hz); IR (KBr) 3060, 2979, 2929, 1595, 1315, 1153, 1109, 800, 661, 580 cm^{-1}. Anal. Calcd for $C_{19}H_{15}IO_2S$: C, 52.55; H, 3.48. Found: C, 52.54; H, 3.52.

General Procedure for Reaction of 3a with Iodine under Photoirradiation: 3a (52.9 mg, 0.15 mmol) and iodine (39.0 mg, 0.15 mmol) in toluene (15 mL) were irradiated with a high-pressure mercury lamp through a Pyrex vessel to be bubbled by nitrogen gas for 1 h. To the reaction mixture was added ethyl acetate (10 mL) and washed with saturated $Na_2S_2O_3$ solution (10 mL × 4). The organic layer was dried with $MgSO_4$, evaporated, and subjected to column chromatography on SiO_2 (chloroform) to give **4a** (65.8 mg, 0.15 mmol) in 100% yield as pale yellow solid.

Reaction of 8 with Iodine Monochloride: To a solution of **8** (18.6 mg, 0.05 mmol) in toluene (5 mL) was added iodine monochloride (16.1 mg, 0.10 mmol), and the resulting mixture was stirred at −20 °C. After being stirred for 19 h, to the reaction mixture was added ethyl acetate (5 mL) and washed with saturated $Na_2S_2O_3$ solution (5 mL × 2). The organic layer was dried with $MgSO_4$ and evaporated to give the brown solid (25.7 mg). The yield (83%) of **9** was determined by the integration of ^{1}H NMR using dibenzyl as an internal standard. The peaks in the ^{1}H NMR spectrum were in good agreement with those of the isolated **9**.

Reaction of a Geometric Mixture of 11: To a solution of lithium diisopropylamide (1.0 mmol, prepared from diisopropylamine (0.11 mL, 1.0 mmol) and *n*-butyllithium (1.59 M in hexane, 0.64 mL, 1.0 mmol)) in THF (6 mL) was added methyl 4-(methylthio)crotonate (0.1562 g, 1.0 mmol) at −78 °C, and the resulting mixture was stirred for 10 min at that temperature. 3-Phenylpropynal (0.1191 g, 1.0 mmol) was added to the mixture at the same temperature, and the reaction mixture was stirred for 1 h. Then, acetic anhydride (0.42 mL, 1.2 mmol) was added at that temperature, and the mixture was gradually warmed up to room temperature. After being stirred for 1 h, DBU (0.2 mL, 1.3 mmol) and THF (2 mL) were added to the mixture and stirred for 30 min. The usual workup (quenching with saturated NH_4Cl solution, extraction with Et_2O, and evaporation) gave yellow oil (0.3317 g). This oil was subjected to short-path column chromatography on SiO_2 (hexane/ethyl acetate = 4:1) to give yellow oil (0.1927 g). The ratio and yield of **11** and its geometric isomers were determined by ^{1}H NMR analysis with the internal method using triphenylmethane as a standard: 0.41 mmol, 41% yield; (1*E*,3*E*):(1*E*,3*Z*):(1*Z*,3*E*):(1*Z*,3*Z*) = 50:28:5:17. The obtained mixture (0.1905 g, 0.41 mmol) was dissolved in toluene (50 mL), and the solution was bubbled by nitrogen gas for 20 min. Iodine (0.2530 g, 1.0 mmol) was added to that solution, and the resulting mixture was irradiated with a high-pressure mercury lamp through a Pyrex vessel for 1.5 h. The usual workup and short-path column chromatography was achieved to give yellow oil (0.2113 g). The yield (0.33 mmol, 80%) of **12** was determined by ^{1}H NMR analysis with the internal method using triphenylmethane as a standard.

Supporting Information Available: Procedures, spectral data of ^{1}H NMR and IR, elemental analytical data, the copies of ^{1}H NMR spectra for **3a**, **3a′**, **3b**, **3c**, **3d**, **3e**, **7**, **8**, **11**, **4a**, **4b**, **4c**, **4d**, **4e**, **9**, and **12**, and crystallographic data of **4a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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