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Synthetic study of *vic*-bromination of diarylacetylenes, easy purification and separation

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Full Research Paper

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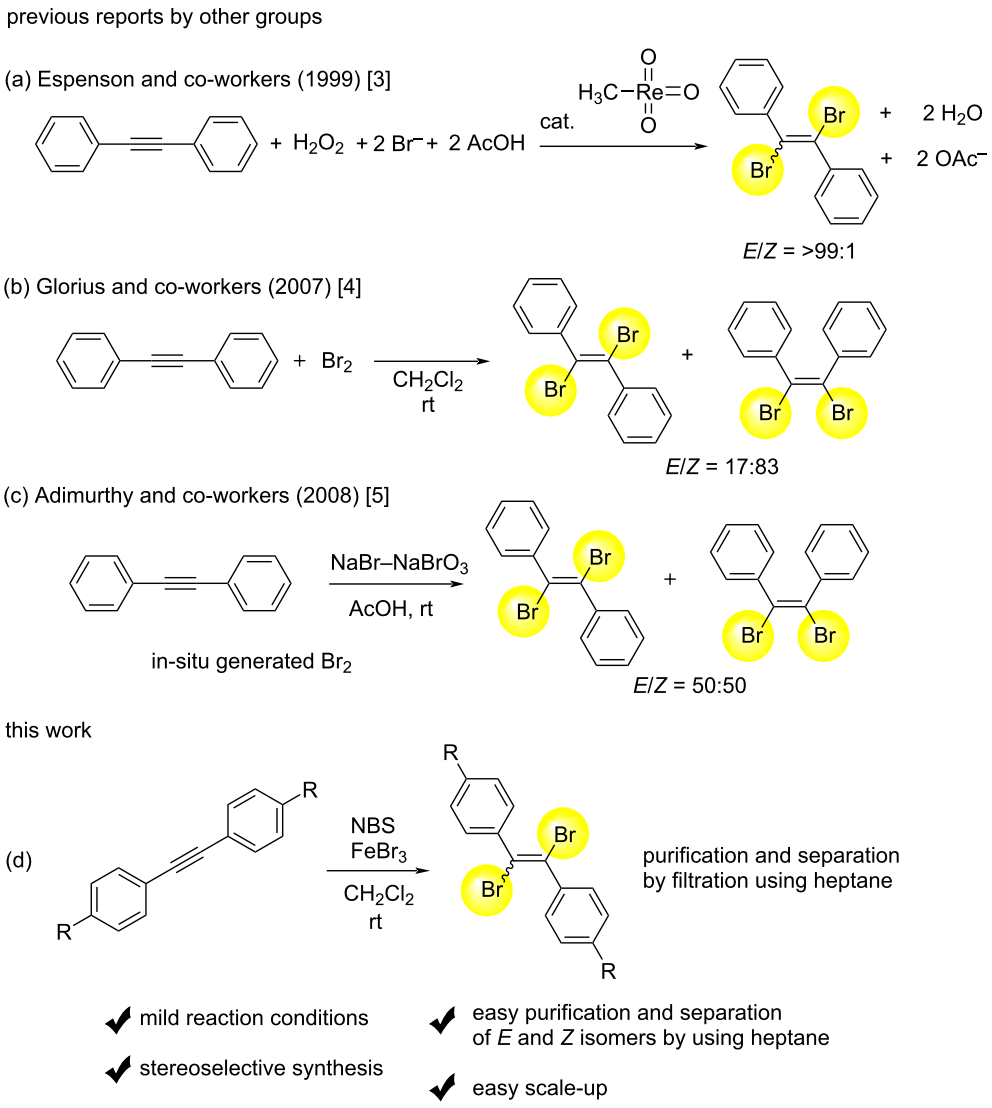
Abstract

E-Selective bromination for diphenylacetylene was established by using the combination of NBS and $FeBr_3$ in CH_2Cl_2. In addition, easy purification and separation from the crude product were found. When the crude product was treated with heptane, the *E* isomer could be recovered as a solid material by utilizing the difference in solubility. On the other hand, the *Z* isomer could be removed by filtration while remaining in solution.

Introduction

The addition reaction of bromine to diphenylacetylene is one of basic reactions and is recognized as important, because resulting 1,2-dibromo-1,2-diphenylethylene can serve as a precursor for various molecular transformations in organic synthesis [1,2]. This reaction seems to be simple, but some reported studies suggest that it is surprisingly difficult to obtain the *E* isomer selectively (Scheme 1). For selected examples, Espenson and co-workers reported in 1999 that *E*-selective bromination of diphenylacetylene took place by using H_2O_2, NaBr, and AcOH in the presence of MTO (methyltrioxorhenium(VII)) to give (*E*)-1,2-dibromo-1,2-diphenylethylene, selectively (Scheme 1a) [3]. However, MTO is an expensive reagent and a more versatile synthetic method is highly needed. As a simple method, the reaction of diphenylacetylene and Br_2 in CH_2Cl_2 was reported by Glorius in 2007 [4], but the selectivity was reported for the *Z* isomer (Scheme 1b). As another example in 2008, Adimurthy and co-workers proposed the combination of NaBr-$NaBrO_3$ in AcOH in order to prepare in-situ generated Br_2, which was reacted with diphenylacetylene to give no selectivity between *E* and *Z* isomers of 1,2-dibromo-1,2-diphenylethylenes (Scheme 1c) [5]. Previous studies reported the selective synthesis of (*E*)-1,2-dibromo-1,2-diphenylethylene and related compounds, but Br_2 or expensive reagent, which was difficult to handle, was often used [6-15].



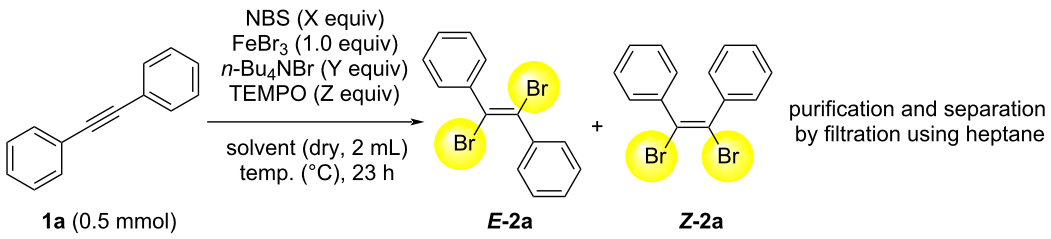
Scheme 1: Selected and previous reports for bromination of diphenylacetylenes (a–c), and this work (d).

Based on these research backgrounds, we have also been interested in the selective synthesis of the *E* isomer of 1,2-dibromo-1,2-diphenylethylene, together with simple purification and separation toward process chemistry, because the compound is an attractive synthetic intermediate for further transformations. During the course of our studies, we have found that the combination of NBS (*N*-bromosuccinimide) and $FeBr_3$ in CH_2Cl_2 was good for the reaction with diphenylacetylene [16-19] to give 1,2-dibromo-1,2-diphenylethylene with high *E*-selectivity. The present method has some advantages. First, is mild reaction conditions, and second is stereoselective synthesis. In addition, we have found an easy purification and separation method of *E* and *Z* isomers of the crude product by using heptane. The method utilizes the difference in solubility of *E* and *Z* isomers. Because of this technique, the purification, separation, and scale-up were easy to perform. In this paper, we wish to report the details of the results.

Results and Discussion

In order to obtain the *E* isomer of 1,2-dibromo-1,2-diphenylethylene, we have examined the reaction regarding optimized conditions (Table 1). The typical procedure is as follows: the reaction of diphenylacetylene (**1a**, 0.5 mmol) with NBS (*N*-bromosuccinimide, X equiv), $FeBr_3$ (1.0 equiv), *n*-Bu_4NBr (Y equiv), and TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl free radical, Z equiv) in solvent (2 mL) at the desired temperature was conducted for 23 h or 2 h. After the reaction, the typical work-up procedure was carried out and the crude prod-

Table 1: Reaction optimization of bromination reaction of diphenylacetylene (**1a**).



Entry	NBS (X equiv)	*n*-Bu_4NBr (Y equiv)	TEMPO (Z equiv)	Temp. (°C)	Solvent	Ratio of ***E*-2a**/***Z*-2a**/**1a**[a]	Yield (%) of ***E*-2a**[b]
1[c]	2.2	0	0	rt	CH_2Cl_2	86:14:0	78
2[c,d]	**2.2**	**0**	**0**	**rt**	**CH_2Cl_2**	**87:13:0**	**78**
3[d]	1.2	0	0	rt	CH_2Cl_2	88:12:0	79
4	2.2	0	1.0	rt	CH_2Cl_2	91:8:1	77
5[d]	2.2	0.5	1.0	rt	CH_2Cl_2	80:2:18	73
6[d]	2.2	1.0	1.0	rt	CH_2Cl_2	55:0:45	47
7	2.2	1.0	0.2	rt	CH_2Cl_2	88:12:0	79
8	2.2	1.0	0.5	rt	CH_2Cl_2	78:2:20	68
9[e]	2.2	1.0	0	rt	CH_2Cl_2	82:18:0	72
10	2.2	1.0	0.5	40	CH_2Cl_2	85:3:12	70
11	2.2	1.0	0.5	60	$C_2H_8Cl_2$	72:3:25	63
12	2.2	0	0	rt	$C_2H_8Cl_2$	58:42:0	54

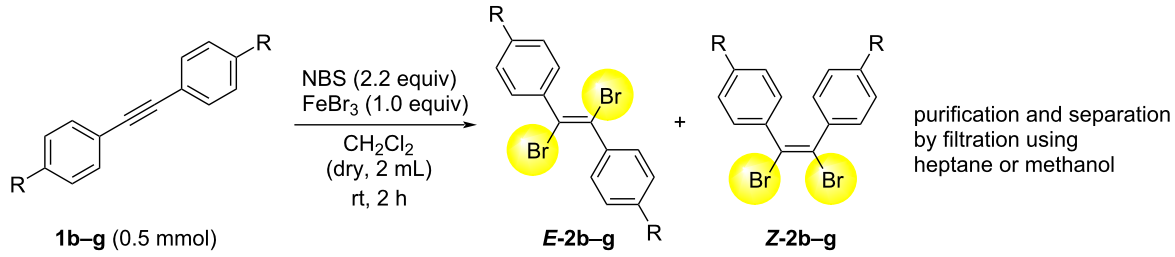
[a]Calculated from the ratio of HPLC area for the crude product. [b]Isolated yield of ***E*-2a** by filtration with heptane from the crude product. The yield of ***E*-2a** was obtained from the solids recovered after the filtration. [c]Reaction time was 2 hours. [d]Calculated from the ratio of GC area for the crude product. [e]Reaction time was 5 hours. $C_2H_8Cl_2$ = 1,2-dichloroethane.

uct was analyzed for the ratio of *E* and *Z* isomers and starting material **1a**, by using HPLC. Purification and separation from the crude product was conducted by the filtration using heptane (Table 1). At first, we have recognized that ***E*-2a** is solid and ***Z*-2a** is liquid in heptane. After various considerations, we found that ***E*-2a** could be isolated by only filtration, utilizing the difference in solubility of ***E*-2a** and ***Z*-2a** in heptane from the crude product.

In Table 1, entry 1, the combination of NBS (2.2 equiv) and $FeBr_3$ (1.0 equiv) for 2 h gave the ratio of ***E*-2a**/***Z*-2a**/**1a** such as 86:14:0 by HPLC, in which ***E*-2a** was obtained in 78% yield. Similarly, to examine the reproducibility of the chemical yield and the ratio of ***E*-2a**/***Z*-2a**/**1a** by GC analysis, Table 1, entry 2 was shown. The reaction time of 2 h gave the same ratio of ***E*-2a**/***Z*-2a**/**1a** by GC analysis, and ***E*-2*a*** was obtained in 78% yield (Table 1, entry 2). The use of a smaller amount of NBS (1.2 equiv) did not result in a decrease of yield, indicating that $FeBr_3$ is thought to be one of the sources of bromine (Table 1, entry 3). To increase the chemical yield and ratio of ***E*-2a**/***Z*-2a**/**1a**, various parameters such as NBS, *n*-Bu_4NBr, TEMPO, temperature, and solvent were examined (Table 1, entries 3–12). Because there was a possibility that a bromine radical was involved, TEMPO was used for the purpose of the ratio-control of *E* and *Z* isomers. TEMPO was found to have a tendency to suppress the generation of ***Z*-2a** in CH_2Cl_2 (Table 1, entries 6 and 8) [20]. Among Table 1, entries 5–11, the addition of *n*-Bu_4NBr did not seem to have any effect. Instead of CH_2Cl_2, $C_2H_8Cl_2$ (1,2-dichloroethane) was used as the solvent, but the yield of ***E*-2a** was decreased (Table 1, entries 11 and 12). Generally, decomposition of the product or over reaction was not observed by GC and/or GC–MS analysis, in the case of the longer reaction time of 23 h. We have examined other Lewis acids such as $ZnBr_2$, LiBr, and $FeBr_2$ instead of the use of $FeBr_3$ under similar reaction conditions. The use of $ZnBr_2$ for reaction time of 4 h showed a ratio of ***E*-2a**/***Z*-2a**/**1a** = 86:14:0 by HPLC analysis and 68% yield of ***E*-2a**. In the case of LiBr, the desired reaction progressed only slightly, even after two days, and the ratio of ***E*-2a**/***Z*-2a**/**1a** = 17:3:80 was indicated by GC analysis. In addition, the use of $FeBr_2$ for a reaction time of 3 h gave an ***E*-2a**/***Z*-2a**/**1a** ratio of 67:13:20 by GC analysis and 57% yield of ***E*-2a**. Based on these investigations, we have adopted the conditions of Table 1, entry 2, because better chemical yield of ***E*-2a** as well as a higher ratio of ***E*-2a**/***Z*-2a**/**1a** with short reaction time were attractive for chemical synthesis in the laboratory [21].

Next, we have investigated the scope and limitations by using various diarylacetylenes bearing the substituents on the benzene ring at *para*-position. The results were summarized in Table 2. Depending on the product's characteristics, either heptane or methanol was used for purification and separation. The reaction of 1,2-di-*p*-tolylethyne (**1b**) under the optimized conditions gave the corresponding product with a ratio of 68:32 of *E* and *Z* isomers. The isolated yield of ***E*-2b** was <54% yield (Table 2, entry 1). Likewise, 1,2-bis(4-(*tert*-butyl)phenyl)ethyne (**1c**) showed the similar tendency to give ***E*-2c** in 45% yield

Table 2: Scope and limitations for bromination of various diarylacetylenes **1**.



1b–g (0.5 mmol) ***E*-2b–g** ***Z*-2b–g**

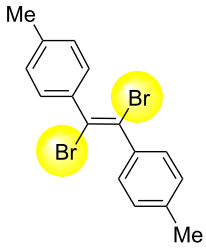
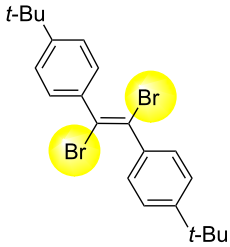
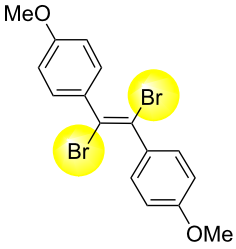
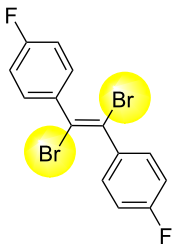
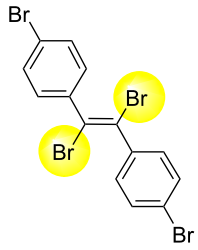
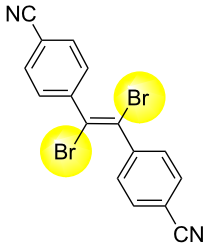
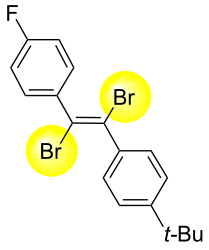
Entry	Product	Ratio of ***E*-2**/***Z*-2**[a]	Yield (%) of ***E*-2**
1[b]	 ***E*-2b**	68:32	<54[c]
2[b]	 ***E*-2c**	57:43	45
3[b]	 ***E*-2d**	82:18	75
4[b]	 ***E*-2e**	89:11	56

Table 2: Scope and limitations for bromination of various diarylacetylenes **1**. (continued)

5[d]	 ***E*-2f**	89:11	78
6[b]	 ***E*-2g**	82:18[e]	70
7[b]	 ***E*-2h**	78:22	41

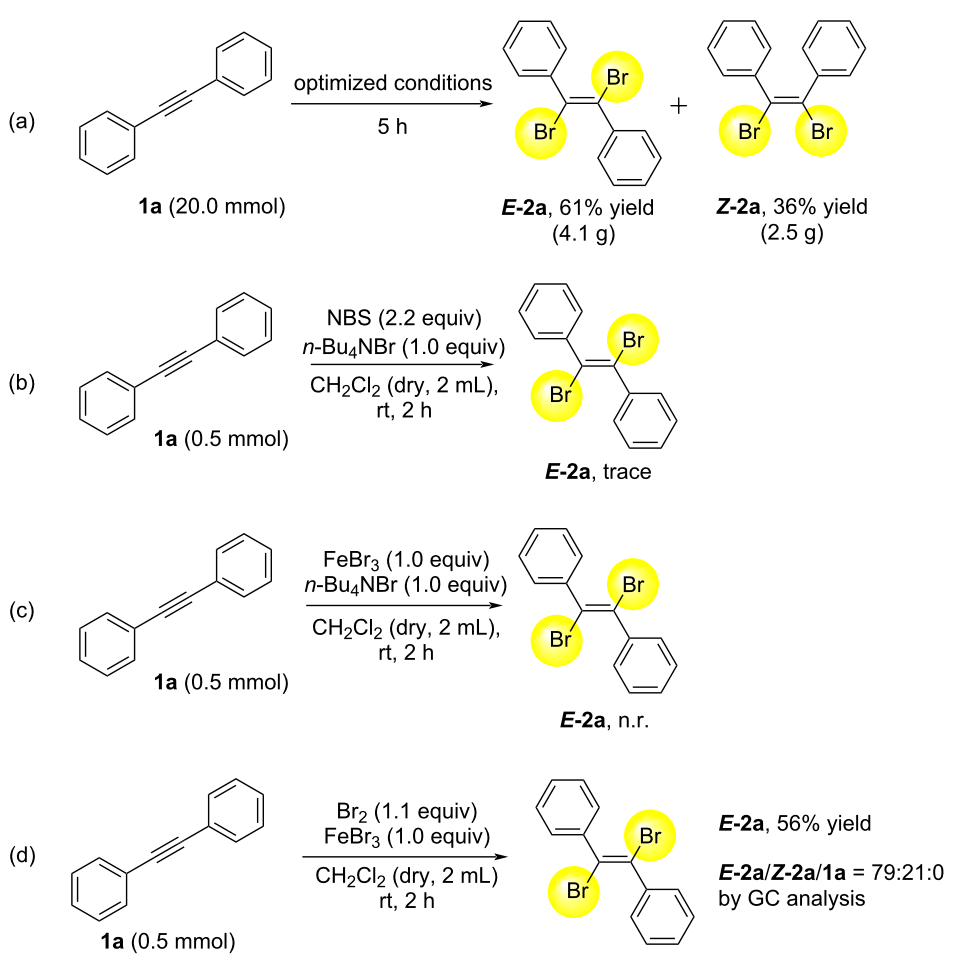
[a]Calculated from the ratio of GC area for crude product. [b]Isolated yield of *E*-isomer by filtration with methanol. [c]Because a small amount of impurity after the isolation was confirmed, the chemical yield was expressed as "<54% yield". See NMR spectra in Supporting Information File 1. [d]Isolated yield of *E*-isomer by filtration with heptane. [e]Calculated from the ratio of ^{1}H NMR for crude product.

(Table 2, entry 2). Poor selectivity as shown in entries 1 and 2 might be due to the stability of the intermediate. In the cases of Table 2, entries 3–6 residues such as MeO, F, Br and CN as the substituent at *para* position of the benzene ring in **1d**–**g**, the selectivity of *E* and *Z* and the isolated yield of the *E* isomer seemed to be good. In the case of unsymmetrical diarylacetylene, 1-(*tert*-butyl)-4-((4-fluorophenyl)ethynyl)benzene (**1h**) was tested and the corresponding ***E*-2h** was isolated and purified with MeOH. ***E*-2h** was obtained in 41% yield (Table 2, entry 7).

A gram-scale synthesis of ***E*-2a** and ***Z*-2a** from **1a** was performed (Scheme 2a). **1a** (20.0 mmol) was allowed to react under optimized conditions for 5 hours. The purification and separation by using heptane from the crude product afforded ***E*-2a** (4.1 g, 12.2 mmol, 61% yield) and ***Z*-2a** (2.5 g, 7.2 mmol, 36% yield), indicating that purification and separation by heptane make scale-up very easy. The *E*-selectivity was dropped in gram-scale synthesis, although the reason is unclear at present.

For the understanding of the reaction mechanism, some control experiments were carried out. The reaction of **1a** with NBS and n-Bu_4NBr without $FeBr_3$ gave trace amount of ***E*-2a** (Scheme 2b). In addition, the reaction of **1a** with $FeBr_3$ and n-Bu_4NBr without NBS showed no reaction (Scheme 2c). Instead of NBS, Br_2 (1.1 equiv) was reacted with **1a** and $FeBr_3$ (1.0 equiv) to give ***E*-2a** in 56% yield, with a ratio of ***E*-2a**/***Z*-2a**/**1a** = 79:21:0. These results indicate that the combination of NBS and $FeBr_3$ might be important and in situ Br_2 might be generated and formed. $FeBr_3$ might react with Br_2 to form $[FeBr_4]^-$ and "Br^+", which can react with **1a**.

As for the reaction mechanism, the plausible pathway might be the following (Scheme 3). The reaction of NBS and $FeBr_3$ might generate Br_2 or "Br^+", which can react with **1a** to form intermediate **A**. **A** reacts with Br^- to give ***E*-2a**. Another possibility is the reaction of NBS and $FeBr_3$ gives coordinated intermediate **B**, which can react with **1a** to give **A**, leading to the formation of ***E*-2a** [21,22]. Both pathways may be mixed together. One reason why *E* and *Z* isomers are formed together



Scheme 2: Gram-scale synthesis of (a), and control experiments of (b), (c) and (d). n.r. = no reaction.

might be due to the equilibrium between **A** and **C**, although there are many unknown points.

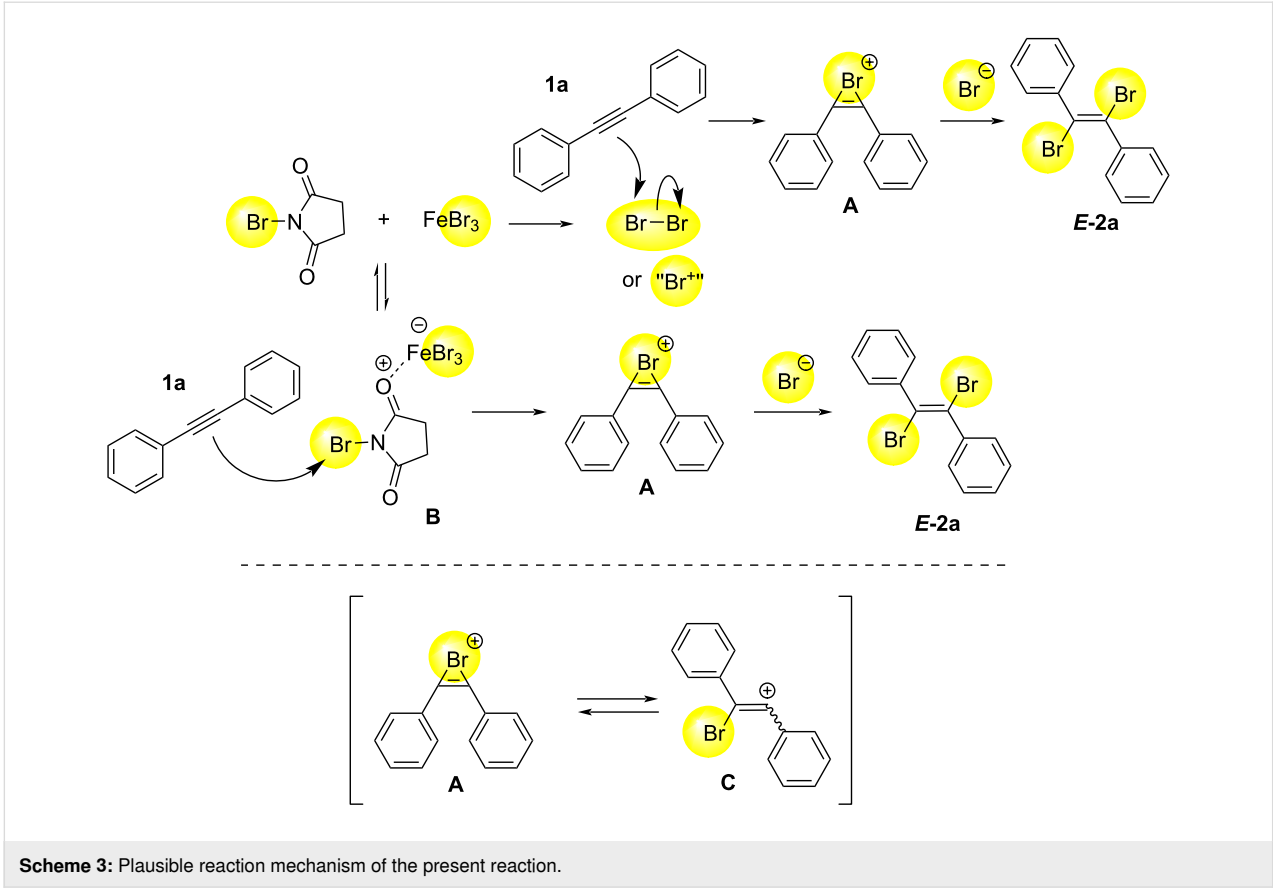
Conclusion

In summary, we have developed a simple and selective procedure of the synthesis of (*E*)-1,2-dibromo-1,2-diphenylethylene from diphenylacetylene by using NBS and $FeBr_3$ in CH_2Cl_2. In addition, heptane played an important and critical role for purification and separation of the crude product. Scope and limitations for bromination of various diarylacetylenes together with the gram-scale synthesis and control experiments were also investigated. These results and findings can contribute to process chemistry for the synthesis of (*E*)-1,2-dibromo-1,2-diphenylethylene and their derivatives. Further synthetic investigations are currently underway in our laboratory.

Experimental

The experimental procedures and characterization data (Table 1, entry 1). The glass flask was dried and heated by a heating gun. After cooled to room temperature, the flask was filled with N_2. $FeBr_3$ (154.2 mg, 0.52 mmol) and NBS (*N*-bromosuccinimide, 196.0 mg, 1.10 mmol) were added to the glass flask. Then, CH_2Cl_2 (dry, 2.0 mL) and 1,2-diphenylacetylene (**1a**, 89.4 mg, 0.502 mmol) were added and the mixture was stirred at room temperature for 2 hours. A 10% aqueous solution of $Na_2S_2O_3$ (20 mL) was added to stop the reaction. The mixture was extracted with CH_2Cl_2 (20 mL × 1), and separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL × 2). The combined organic phase was washed with H_2O (20 mL) and brine (20 mL), and dried over Na_2SO_4. After this, filtration and concentration were performed; the organic phase was passed through a short column of silica gel using CH_2Cl_2 (100 mL) to remove inorganic materials and others; then it was concentrated under reduced pressure to give the crude product. This crude product was purified three times with heptane to obtain (*E*)-1,2-dibromo-1,2-diphenylethylene (***E*-2a**, 132.6 mg, 0.392 mmol, 78% yield) of high-purity.

(*E*)-1,2-Dibromo-1,2-diphenylethylene (*E*-2a) [4]: White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.46 (m, 6H),



Scheme 3: Plausible reaction mechanism of the present reaction.

7.50–7.57 (m, 4H) ppm; ^{13}C NMR (100 MHz $CDCl_3$) δ 118.0, 128.4, 128.9, 129.1, 140.7 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{10}Br_2Na$, 358.9041; found, 358.9028.

(*Z*)-1,2-Dibromo-1,2-diphenylethylene (*Z*-2a) [7]: Yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.22 (m, 10H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.7, 128.0, 128.3, 129.8, 139.4 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{11}Br_2$, 336.9222; found, 336.9215.

Supporting Information

Supporting Information File 1

General remarks, preparation of substrates, experimental procedure, characterization data of compounds, and copies of ^{1}H and ^{13}C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-22-61-S1.pdf]

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Author Contributions

Akane Togo: conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft. Hiyono Suzuki: conceptualization; formal analysis; investigation; methodology. Yuto Akai: formal analysis; methodology; supervision; validation. Makoto Matsumoto: formal analysis; methodology; supervision; validation. Yoshinori Suzuma: methodology; project administration; supervision. Hidehiko Kodama: funding acquisition; methodology; project administration; supervision. Kouichi Matsumoto: conceptualization; funding acquisition; methodology; project administration; supervision; validation; visualization; writing – original draft.

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Data Availability Statement

All data that supports the findings of this paper is available in the published article and/or the supporting information to this article.

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