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DIELS-ALDER REACTION AND DOUBLE PHENYLATION IN REACTION OF THIOPHENES WITH DIPHENYLIODONIUM TRIFLATE

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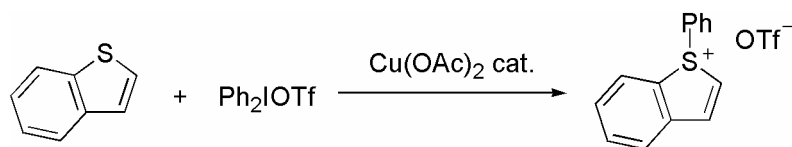
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Abstract – The reaction of 2,5-dimethylthiophene with diphenyliodonium triflate in the presence of *N*-phenylmaleimide and a catalytic amount of Cu(OAc)₂ gave 1:1 and 1:2 cycloadducts with *N*-phenylmaleimide. The similar reactions of 2,5-bis(trimethylsilyl)thiophene, 3-phenylthiophene, and thiophene afforded 2,5-diphenylthiophene, 2,3,5-triphenylthiophene, and 2,5-diphenylthiophene, respectively. The cycloadducts and 2,5-diphenylated thiophenes are considered to be formed *via* *S*-phenylation of thiophenes affording 1-phenylthiophenium triflates.

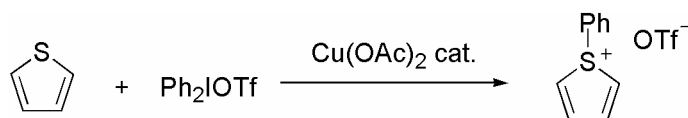
In the previous papers,¹ we reported a convenient synthesis of 1-phenyl-1-benzothiophenium triflates by a direct *S*-phenylation of benzothiophenes with diphenyliodonium triflate, as shown in Scheme 1. To date, however, there have been reported only two examples by Furukawa² and Lee³ on the synthesis of 1-phenylthiophenium salts. These papers deal with the reaction of thiophene 1-oxides² or manganese thiophene tricarbonyl complexes.³

This paper is dedicated to Dr. Pierre Potier on the Occasion of his 70th birthday.

If the *S*-phenylation of thiophenes occurs in the same way as that of benzothiophenes,⁴ it is expected that 1-phenylthiophenium salts are formed (Scheme 2). Thus, we have examined the reaction of thiophenes with diphenyliodonium triflate in the presence of a copper catalyst. In this paper, we wish to report the Diels-Alder reaction and double phenylation *via* the *in situ*-generated 1-phenylthiophenium salts.



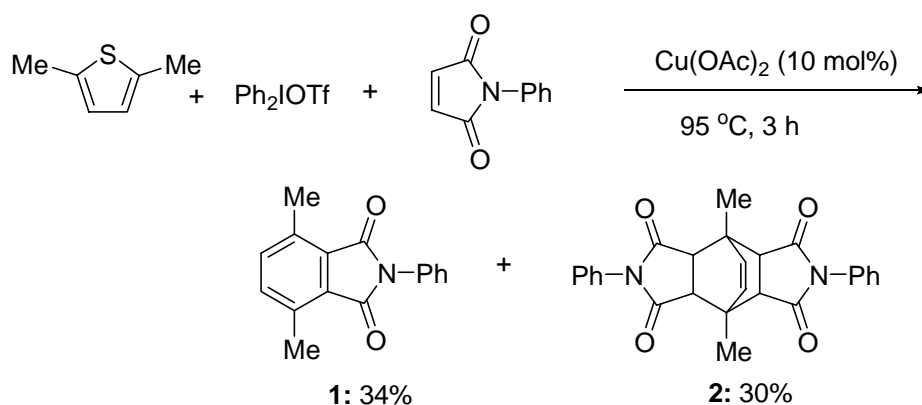
Scheme 1



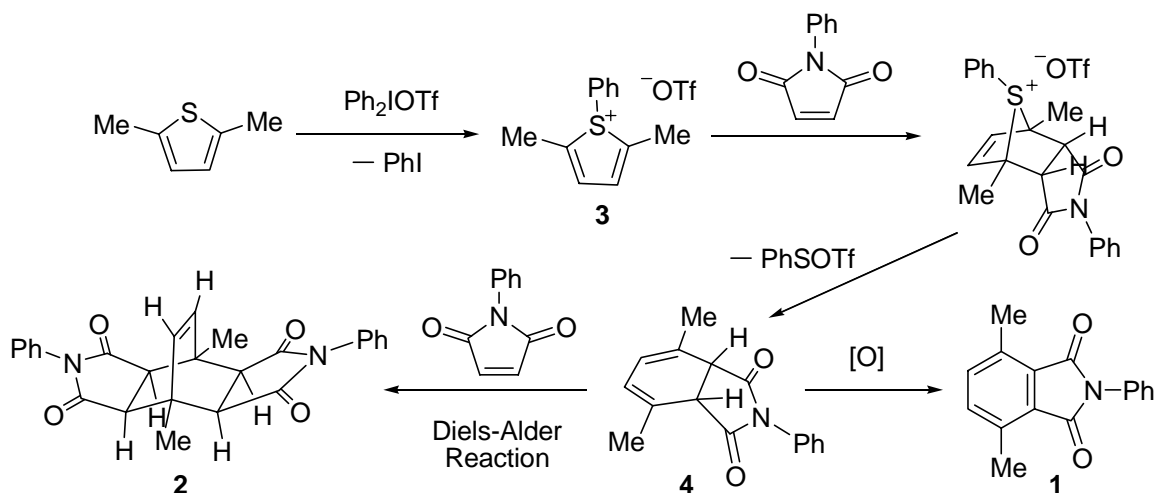
Scheme 2

First, we attempted to isolate 1-phenylthiophenium triflates by the reaction of thiophenes with diphenyliodonium triflate. A mixture of a thiophene (thiophene, 2,5-dibromothiophene, 2,5-dimethylthiophene, or 2,5-diphenylthiophene) and diphenyliodonium triflate was heated in the presence of $\text{Cu}(\text{OAc})_2$ (10 mol%) at 130 °C for 0.5 h but no 1-phenylthiophenium triflates were isolated. Next, we examined the trapping reaction of the *in situ*-generated 1-phenylthiophenium salts with *N*-phenylmaleimide since the isolation was failed in the reaction under the above conditions. A mixture of 2,5-dimethylthiophene, diphenyliodonium triflate, and *N*-phenylmaleimide in the presence of 10 mol% $\text{Cu}(\text{OAc})_2$ was heated at 95 °C for 3 h. The reaction mixture was separated by column chromatography on silica gel. As shown in Scheme 3, the isolated products were a 1:1 cycloadduct, 3,6-dimethyl-*N*-phenylphthalimide (**1**) (34%), and a 1:2 cycloadduct, 1,4-dimethylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid bis(phenylimide) (**2**) (30%). The structures of the products were determined by ^1H and ^{13}C NMR spectrometry. The detailed structure of the 1:2 cycloadduct **2** was further confirmed by a single crystal X-Ray analysis.

The formation of 1:1 cycloadduct (**1**) was reported by the reaction of 2,5-dimethylthiophene 1-oxide with *N*-phenylmaleimide.⁵ In the present reaction, the intermediacy of the similar type of diene species, that is, 2,5-dimethyl-1-phenylthiophenium triflate (**3**), is suggested by the formation of 1:1 cycloadduct **1**, which should be derived from the corresponding 1,2-dihydro-3,6-dimethyl-*N*-phenylphthalimide (**4**), as shown in Scheme 4.



Scheme 3



Scheme 4

Similarly, the formation of **4** easily explains the route to the 1:2 adduct **2** because the 1:2 adduct **2** is formed by the subsequent Diels-Alder reaction with *N*-phenylmaleimide.

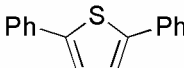
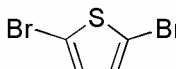
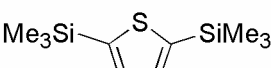
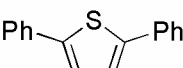
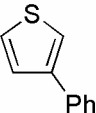
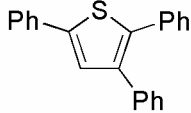
In the present study, the endo-endo bisadduct **2** was formed solely as the 1:2 cycloadduct. The endo-exo isomer was not obtained. In the similar cycloaddition of 3,4-di-*tert*-butylthiophene 1,1-dioxide with *N*-phenylmaleimide, a mixture of the endo-endo bisadduct (58%) and the endo-exo bisadduct (40%) was formed.⁶ The difference between these results is attributable to the steric hindrance of *tert*-butyl group.

In the present case, the lack of the sterically hindered *tert*-butyl group favors the endo mode of addition.

On the other hand, the similar reactions using other thiophenes did not give the cycloadducts. The results are summarized in Table 1. No products with diphenyliodonium triflate or *N*-phenylmaleimide were formed when 2,5-diphenylthiophene or 2,5-dibromothiophene was reacted with diphenyliodonium triflate in the presence of *N*-phenylmaleimide. However, the reaction of 2,5-bis(trimethylsilyl)thiophene under the same conditions did not give the cycloadduct with *N*-phenylmaleimide but led to the formation of 2,5-diphenylthiophene (58% yield). Apparently, in the reaction of 2,5-bis(trimethylsilyl)thiophene, trimethylsilyl group is cleaved and replaced by phenyl group. Since the generation of acids is

well-known in the decomposition of diphenyliodonium salts,⁷ trifluoromethanesulfonic acid (TfOH) generated *in situ* can cleave the silyl group by protonation. Therefore, it is considered that 2,5-bis(trimethylsilyl)thiophene is first converted into thiophene by the *in situ*-generated TfOH and then double-phenylated to lead to 2,5-diphenylthiophene.⁸

Table 1. Reaction of thiophenes with Diphenyliodonium Triflate.^a

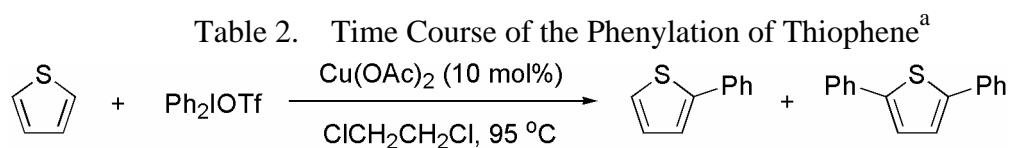
Thiophene	Product	Yield (%) ^b
	—	—
	—	—
		58
		58

(a) A mixture of thiophene (2.0 mmol), diphenyliodonium triflate (4.0 mmol), *N*-phenylmaleimide (2.0 mmol), and Cu(OAc)₂ (0.2 mmol) was heated at 95 °C for 3 h. (b) Isolated yield.

In order to confirm this hypothesis, the reaction of 3-phenylthiophene was conducted. The reaction of 3-phenylthiophene with diphenyliodonium triflate under the same conditions actually gave 2,3,5-triphenylthiophene in 58% yield. Therefore, this result indicates that the α position of thiophenes is easily subject to phenylation by the reaction with diphenyliodonium triflate.

The double phenylation is considered to proceed with a stepwise phenylation. The time course of the phenylation of thiophene was examined at 95 °C. The results are summarized in Table 2.

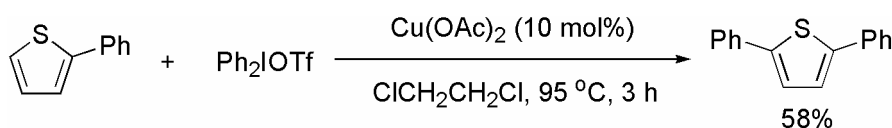
Table 2 shows that the double phenylation proceeds very rapidly at the given reaction conditions: thiophene (0.5 mmol), diphenyliodonium triflate (4.0 mmol), Cu(OAc)₂ (0.05 mmol), 1,2-dichloroethane (1.8 mL), and 95 °C. When the amount of diphenyliodonium triflate was decreased from 4.0 mmol to 2.5 mmol, the phenylation reaction of thiophene for 0.25 h gave 2-phenylthiophene and 2,5-diphenylthiophene in 20 and 24% yields, respectively.



Entry	Time (h)	Yield (%) ^b	
		2-Phenylthiophene	2,5-Diphenylthiophene
1	0.25	6	38
2	0.5	4	36
3	1	0	39
4	2	0	47
5	3	0	50
6 ^c	0.25	20	24

(a) A mixture of thiophene (0.50 mmol), diphenyliodonium triflate (4.0 mmol), Cu(OAc)₂ (0.05 mmol) in dichloroethane (1.8 mL) was heated at 95 °C. (b) GC yields based on thiophene. (c) Diphenyliodonium triflate (2.5 mmol) was used.

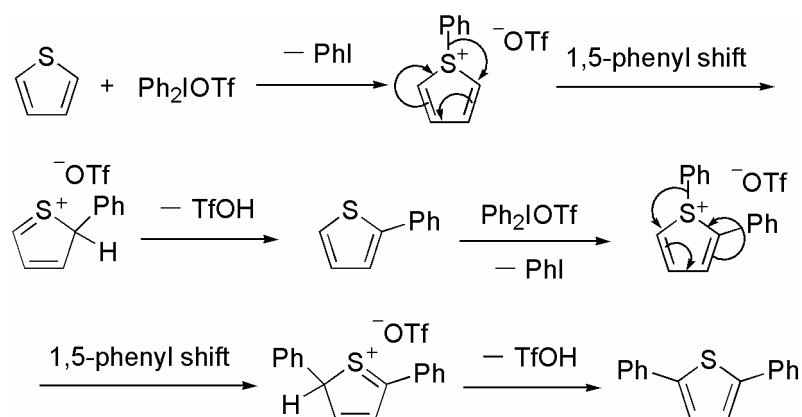
Expectedly, the phenylation reaction of 2-phenylthiophene under the same conditions (95 °C, 3 h) afforded 2,5-diphenylthiophene in 58% yield (Scheme 5).



Scheme 5

From the above results, phenylation at the α position of thiophenes proceeds *via* *S*-phenylation giving 1-phenylthiophenium triflate, followed by phenyl migration and deprotonation. The ease of the phenyl migration in the case of 1-phenylthiophenium salts may be due to the instability, because the corresponding benzo derivative, 1-benzothiophene, affords a stable 1-phenyl-1-benzothiophenium triflate, which undergoes the phenyl migration when it is heated at a high temperature (170-180 °C).⁹ The subsequent phenylation and migration of the phenyl group finally afford 2,5-diphenylthiophene, as shown in Scheme 6.

In summary, we have found that the reaction of thiophenes with diphenyliodonium triflate in the presence of Cu(OAc)₂ provides the products derived from the *S*-phenylation reaction. The observed reactions of the *in situ*-generated 1-phenylthiophenium triflates are cycloaddition with *N*-phenylmaleimide and phenyl migration. The former reaction gives the 1:1 cycloadduct and the 1:2 cycloadduct, while the latter provides 2,5-diphenylthiophenes by double phenylation. These behaviors are attributed to the instability due to the lack of the aromaticity.



Scheme 6

EXPERIMENTAL

General. Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. ¹H and ¹³C NMR spectra were taken with a JEOL JNM-AL 300 spectrometer. GLC analyses were performed on a Shimadzu GC-9A with a flame ionization detector by using a 1.6 m x 2.6 mm glass column packed with a 5% Silicon OV-17 on 60/70 mesh Chromosorb W. Elemental analysis was conducted by the Service Center of the Elemental Analysis of Organic Compounds, Faculty of Science, Kyushu University.

Diphenyliodonium triflate,¹⁰ 2,5-diphenylthiophene,¹¹ and 2,5-bis(trimethylsilyl)thiophene¹² were prepared according to the literatures. Other chemicals were purchased commercially and used as received.

Reaction of 2,5-Dimethylthiophene with Diphenyliodonium Triflate in the Presence of *N*-Phenylmaleimide and Cu(OAc)₂.

A mixture of 2,5-dimethylthiophene (0.22 g, 2.0 mmol), diphenyliodonium triflate (1.72 g, 4.0 mmol), *N*-phenylmaleimide (0.35 g, 2.0 mmol), and Cu(OAc)₂ (0.04 g, 0.2 mmol) was heated with stirring at 95 °C for 3 h. The reaction mixture was submitted to column chromatography on silica gel and separated with hexane and dichloromethane (1:1) as an eluent to afford 3,6-dimethyl-*N*-phenylphthalimide and 1,2-dimethylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid bis(phenylimide).

3,6-Dimethyl-*N*-phenylphthalimide (0.171 g, 34%): mp 133-135 °C (CH₂Cl₂-hexane) (lit.,¹³ 133-134 °C); ¹H NMR (CDCl₃, 300 MHz) δ 2.70 (s, 6 H, Me), 7.38-7.49 (m, 7 H, ArH); ¹³C NMR (CDCl₃, 75 MHz) δ 17.5, 126.7, 127.8, 128.4, 128.5, 128.9, 135.9, 136.4, 168.0.

1,4-Dimethylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid bis(phenylimide) (0.256 g, 30%): mp 229-235 °C (CH₂Cl₂-hexane); ¹H NMR (CDCl₃, 300 MHz) δ 1.99 (s, 6 H, Me), 2.90 (s, 4 H, CH), 6.07 (s, 2 H, =CH), 7.15-7.48 (m, 10 H, ArH); ¹³C NMR (CDCl₃, 75 MHz) δ 19.6, 40.2, 49.6, 126.5, 128.8, 129.1, 131.5, 135.1, 174.2. Anal. Calcd for C₂₆H₂₂N₂O₄: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.26; H,

5.39; N, 6.60. The further structural evidence was obtained by a single crystal X-Ray analysis. A single crystal of the 1:2 cycloadduct for an X-Ray analysis was obtained by slow evaporation of acetone/ether (1:1). Data were collected on a Mac Science MXC3K diffractometer. All diagrams and calculations were performed using CRYSTAN-GM software package (MacScienc, Japan). Crystal data for the 1:2 cycloadduct: $C_{26}H_{22}N_2O_4$, $M_r = 426.50$, triclinic, space group $P1$, $a = 7.620(2) \text{ \AA}$, $b = 15.701(5) \text{ \AA}$, $c = 19.091(6) \text{ \AA}$, $\alpha = 107.57(3)^\circ$, $\beta = 90.74(3)^\circ$, $\gamma = 91.36(3)^\circ$, $V = 2176.4(1) \text{ \AA}^3$, $Z = 4$, $D_x = 1.301 \text{ Mg m}^{-3}$, $D_m = 1.2000 \text{ Mg m}^{-3}$, Mo $K\alpha$ radiation $\lambda = 0.71073 \text{ \AA}$, $R = 0.151$ ($R_w = 0.154$) for 3124 unique data with $F_o > 3.00\sigma(I)$ and 257 variables. Attempts to obtain a better crystal were unsuccessful. The stereostructure is shown in Figure 1.

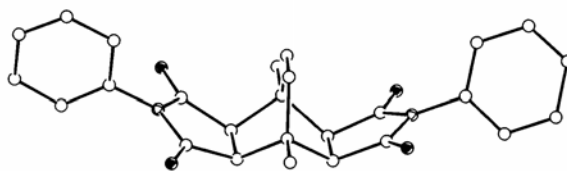


Figure 1

Reaction of Other Thiophenes with Diphenyliodonium Triflate in the Presence of *N*-phenylmaleimide and $Cu(OAc)_2$. Other thiophenes such as 2,5-diphenylthiophene, 2,5-dibromothiophene, 2,5-bis(trimethylsilyl)thiophene, and 3-phenylthiophene were reacted with diphenyliodonium triflate in the presence of *N*-phenylmaleimide and $Cu(OAc)_2$ under the same conditions as above. In the reactions of 2,5-bis(trimethylsilyl)thiophene and 3-phenylthiophene, 2,5-diphenylthiophene (58%) and 2,3,5-triphenylthiophene (58%), respectively, were obtained.

2,5-Diphenylthiophene: mp 153-155 °C (MeOH) (lit.,¹¹ 152-153 °C); 1H NMR ($CDCl_3$, 300 MHz) δ 7.23-7.40 (m, 10 H, ArH), 7.60-7.63 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 123.9, 125.6, 127.5, 128.9, 134.3, 143.6.

2,3,5-Triphenylthiophene: mp 142-143 °C (CH_2Cl_2 -hexane) (lit.,¹⁴ 142-143 °C); 1H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.42 (m, 14 H, ArH), 7.65 (d, $J = 8$ H, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 125.6, 126.5, 127.0, 127.4, 127.6, 128.4, 128.5, 128.9, 129.06, 129.13, 134.1, 134.2, 136.6, 137.9, 138.9, 142.5.

Phenylation of Thiophene or 2-Phenylthiophene with Diphenyliodonium Triflate in the Presence of $Cu(OAc)_2$. A thiophene (0.5 mmol), diphenyliodonium triflate (4.0 or 2.5 mmol), $Cu(OAc)_2$ (0.05 mmol), and 1,2-dichloroethane (1.8 mL) were placed in a glass tube (1.8 cm x 17 cm) and the glass tube was sealed. The sealed tube was heated at 95 °C for 0.25-3 h. Octacosane was added to the reaction mixture, which was analyzed by GLC. The results are given in Table 2.

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