

Alkenylation of thiophenes at the 2-position with magnesium alkylidene carbenoids

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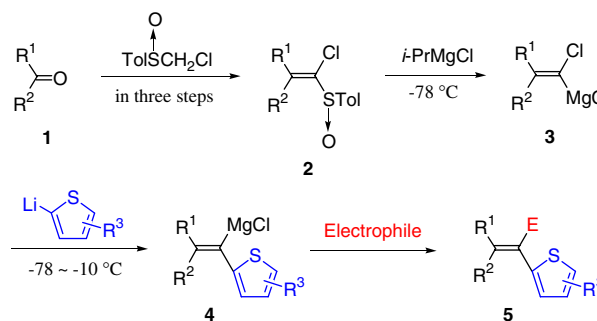
Abstract—Treatment of magnesium alkylidene carbenoids, generated from 1-chlorovinyl *p*-tolyl sulfoxides with isopropylmagnesium chloride at $-78\text{ }^{\circ}\text{C}$ in toluene, with 2-lithiothiophenes gave 2-alkenylated thiophenes in good to high yields. The intermediate of this reaction was found to be an alkenylmagnesium, which could be trapped with iodoalkanes and ethyl chloroformate. This procedure offers a novel and efficient one-pot synthesis of thiophenes having a disubstituted or a trisubstituted olefin at the 2-position from thiophenes in good yields.

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Thiophenes are obviously one of the most important heterocyclic aromatic compounds in organic and synthetic organic chemistry. Thiophene moiety is frequently found in pharmaceuticals.¹ Furthermore, thiophenes are becoming very important compounds in material science, especially in the science of conducting polymer. Polythiophenes are receiving considerable attention these days.²

Thiophenes are known to be relatively highly reactive aromatic compounds and Friedel–Crafts-type reactions (alkylations and acylations) are usually conducted with weak Lewis or Bronsted acid. In contrast to the alkylations and acylations, alkenylations of thiophenes are quite limited and some examples are reported as follows. Heck-type reaction of 2-iodothiophene with olefins.³ Carbosilylation of 2-iodothiophenes with allenes.⁴ Negishi cross-coupling of arylzinc chloride of thiophenes with vinyl tellurides.⁵ Addition of thiophenes to alkynes catalyzed by a dinuclear palladium complex.⁶ Addition of thiophenes to alkynes catalyzed by tetrarhodium dodecacarbonyl.⁷ Palladium-catalyzed alkenylation of thiophene with olefins.⁸

We previously reported a new method for alkenylation of arylamines at the *ortho*-position⁹ and *N*-alkenylation of nitrogen-containing heterocycles¹⁰ utilizing the reaction of magnesium alkylidene carbenoids with *N*-lithio arylamines and *N*-lithio nitrogen-containing heterocycles, respectively, as a key reaction. As the magnesium alkylidene carbenoids are expected to have much ability for alkenylation of many compounds having proper nucleophilicity, we have been continuing to investigate the reaction of magnesium alkylidene carbenoid with some *C*-lithio heteroaromatic compounds. As a result, 2-lithiothiophenes are found to be reactive with the magnesium alkylidene carbenoids to give 2-alkenylthiophenes in good yields as shown in Scheme 1.



Scheme 1.

Keywords: Magnesium alkylidene carbenoid; Sulfoxide–magnesium exchange reaction; Alkenylation; Thiophene; 2-Alkenylthiophene.

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Thus, 1-chlorovinyl *p*-tolyl sulfoxides **2** were synthesized from ketones **1** and chloromethyl *p*-tolyl sulfoxide in three steps in high overall yields.¹¹ Vinyl sulfoxide **2** was treated with *i*-PrMgCl in toluene at $-78\text{ }^{\circ}\text{C}$ to give magnesium alkylidene carbenoid **3** instantaneously. To this magnesium carbenoid a solution of 2-lithiothiophene in THF was added at $-78\text{ }^{\circ}\text{C}$ and the temperature of the reaction mixture was slowly allowed to warm to $-10\text{ }^{\circ}\text{C}$ to give 2-alkenylated thiophene **5** ($\text{E} = \text{H}$) in good to high yield via alkenylmagnesium intermediate **4**. The alkenylmagnesium intermediate **4** was found to be reactive with several electrophiles to afford thiophenes having a fully substituted olefin at 2-position **5** ($\text{E} = \text{alkyl group, ethoxycarbonyl group, etc.}$) in good overall yield from **2**. Details of these results are reported hereinafter.

At first, in order to remove a trace of moisture in the reaction mixture, *t*-BuMgCl (0.13 equiv) was added to a solution of 1-chlorovinyl *p*-tolyl sulfoxide **6**¹¹ in dry THF at $-78\text{ }^{\circ}\text{C}$. *i*-PrMgCl (2.8 equiv) was added to the reaction mixture to afford instantaneously magnesium alkylidene carbenoid **7**. To this solution of the carbenoid was added 2-lithiothiophene, derived from thiophene (3 equiv) and *n*-BuLi (3.3 equiv) in THF, and the reaction mixture was slowly allowed to warm to $-10\text{ }^{\circ}\text{C}$ (Table 1, entry 1). Fortunately, the desired reaction took place to afford 2-alkenylthiophene **8a** in 60% yield.

Because we recognized that this is quite interesting and novel reaction, improvement of the yield of **8a** was investigated and the results are summarized in Table 1. Generation of **7** in toluene worked well; however, as thiophene did not dissolve in toluene, this reaction could not be carried out in toluene (entry 2). Next, magnesium alkylidene carbenoid **7** was generated in toluene and to this was added 2-lithiothiophene (generated in a mixture of toluene–THF 3:1) (entry 3). This reaction gave 78% yield of the desired **8a**.¹² As a result, the reaction was conducted in a mixture of toluene and THF in a ratio of 9:1. We further investigated this reaction with adding an additive (ether-type solvent) expecting for better yields; however, no improvement of the yield was achieved (entries 4–6). So we decided the conditions

Table 2. Reaction of magnesium alkylidene carbenoid **7** with several 2-lithiothiophenes to afford 2-alkenylthiophenes **8**

Entry	2-Lithiothiophenes	Product/ 8	Yield (%)
1			67 ^a
2			77
3			80
4			80

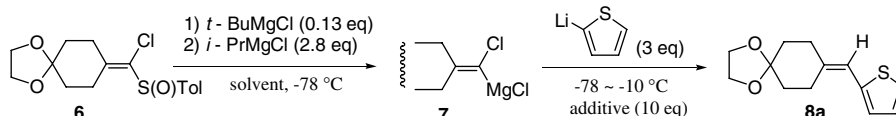
^a 2-Lithiothiophene was generated from benzothiophene with *t*-BuLi.

described in entry 3 as the optimized conditions and used them throughout this study.

Next, generality of this reaction was investigated using several 2-lithiothiophenes and magnesium alkylidene carbenoid **7**, and the results are summarized in Table 2. Benzothiophene gave the desired 2-alkenylthiophene **8b**; however, the yield slightly diminished (entry 1). Thiophenes having an electron-donating group, and also having an electron-withdrawing group gave good yields of the desired 2-alkenylthiophenes **8c–e** (entries 2–4). From these results generality of this reaction was verified.

Based on our previous studies,¹³ the intermediate of this reaction was thought to be alkenylmagnesium **9** (Table 3). To ascertain that the intermediate was the alkenylmagnesium, the reaction between magnesium alkylidene carbenoid **7** and 2-lithiothiophene was quenched with CH_3OD . This reaction afforded deuteriated 2-alkenylthiophene **10** ($\text{E} = \text{D}$) in 78% yield with 97% deuterium incorporation (Table 3, entry 1). From this result, the

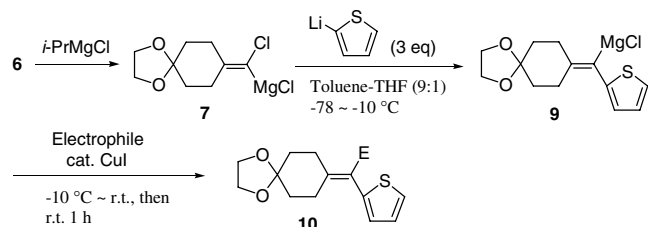
Table 1. Reaction of magnesium alkylidene carbenoid **7**, derived from **6** with *i*-PrMgCl, with 2-lithiothiophene to afford 2-alkenylthiophene **8a**



Entry	Solvent	Additive	8a Yield (%)
1	THF	None	60
2	Toluene	None	— ^a
3	Toluene/THF ^b	None	78
4	Toluene/THF ^b	Et_2O	47
5	Toluene/THF ^b	CPME	37
6	Toluene/THF ^b	DME	27

^a Thiophene did not dissolve in toluene and the desired reaction could not be conducted.

^b The ratio of toluene and THF is 9:1. See the text.

Table 3. Reaction of the alkenylmagnesium intermediate **9** with electrophiles to give thiophene having a fully substituted olefin **10**

Entry	Electrophile (equiv)	CuI (mol %)	E	Yield of 10 (%)
1	CH ₃ OD (excess)	None	D	78 ^a
2	CH ₃ I (3)	5	CH ₃	72
3	CH ₃ CH ₂ I (10)	5	CH ₂ CH ₃	69 ^b
4	CH ₂ =CHCH ₂ I (3)	5	CH ₂ CH=CH ₂	67
5	(CH ₃) ₂ CHI (10)	5	CH(CH ₃) ₂	— ^c
6	PhCH ₂ Br (3)	5	CH ₂ Ph	72
7	I ₂ (10)	None	I	71
8	ClCOOC ₂ H ₅ (10)	None	COOC ₂ H ₅	70
9	PhCHO (10)	None	CH(Ph)OH	— ^c
10	(CH ₃) ₂ CO (10)	None	C(CH ₃) ₂ OH	— ^c
11	PhCOCl (10)	None	COPh	— ^d

^a Deuterium content 97%.^b The reaction mixture was stirred for 3 h at room temperature.^c Compound **8a** was obtained as a main product.^d A complex mixture was obtained.

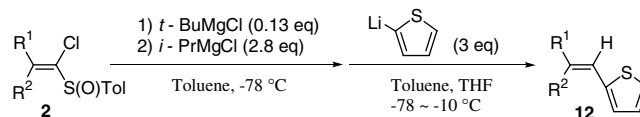
intermediate of this reaction was confirmed to be alkenylmagnesium **9**.

It was thought that if this alkenylmagnesium intermediate **9** could be trapped with electrophiles, a new method

Table 4. Reaction of magnesium alkylidene carbenoid **7** with 2-lithiothiophenes followed by iodomethane in the presence of 5 mol % of Cu(I) iodide to give thiophenes having a fully substituted olefin at the 2-position **11**

Entry	2-Lithiothiophenes	Product 11	Yield (%)
1			58
2			75
3			70
4			77

for a synthesis of thiophenes having a fully substituted olefin would be achieved. At first, iodomethane (10 equiv) was added to the reaction mixture. This reaction gave the methylated product **10** (E = CH₃); however, the yield was not acceptable (54%). After some investigations, fortunately, Cu(I) iodide was found to be effective catalyst in this reaction. Thus, after generation of intermediate **9**, Cu(I) iodide (5 mol %) followed by iodomethane (3 equiv) were added to the reaction

Table 5. Synthesis of 2-alkenylthiophenes **12** from 1-chlorovinyl *p*-tolyl sulfoxides **2** with 2-lithiothiophene

Entry	1-Chlorovinyl <i>p</i> -tolyl sulfoxide	2-Alkenylthiophene 12		
		<i>E/Z</i>	Yield (%)	
1			—	63
2			—	72
3			34/66	60
4			81/19	73

mixture at $-10\text{ }^{\circ}\text{C}$ and the reaction mixture was slowly allowed to warm to room temperature. The stirring was continued for 1 h at room temperature to give the desired methylated product in 72% yield (entry 2).¹⁴

Iodoethane, allyl iodide, benzyl bromide worked well; however, 2-iodopropane did not give the desired product at all (entry 3–6). Iodine and ethyl chloroformate gave iodinated and ethoxycarbonylated product, respectively, in good yield (entries 7 and 8). Benzaldehyde and acetone did not afford the expected adduct but the protonated product **8a** (entries 9 and 10). Benzoyl chloride only gave a complex mixture (entry 11).

Table 4 shows the above-mentioned synthesis of thiophenes having a fully substituted olefin at the 2-position by combination of three components, 1-chlorovinyl *p*-tolyl sulfoxide **6**, 2-lithiothiophenes, and iodomethane. From the results shown in Table 4, it is recognized that the method mentioned above is applicable to various thiophenes. Comparing the yields shown in Table 4 with those in Table 2, it is obvious that the methylation with the alkenylmagnesium intermediates proceeded in high yields.

Finally, the substrate scope of this reaction was investigated using various 1-chlorovinyl *p*-tolyl sulfoxides with 2-lithiothiophene and the results are shown in Table 5. 1-Chlorovinyl *p*-tolyl sulfoxides prepared from cyclopentadecanone and cyclohexanone gave the desired products **12a** and **12b**, respectively, in good yields (entries 1 and 2). Low stereospecificity was observed in the reaction with geometrical isomers **2c** and **2d** (entries 3 and 4). *E*-Vinyl sulfoxide **2c** gave *Z*-olefin **12c** as main product. In contrast to this, *Z*-vinyl sulfoxide **2d** mainly gave *E*-olefin **12d**.¹⁵

In conclusion, we found that the reaction of magnesium alkylidene carbenoids **2** with 2-lithiothiophenes gave thiophenes having an olefin at the 2-position in good yields. Intermediates of these reactions were found to be alkenylmagnesiums and these were trapped with several electrophiles to give thiophenes having fully substituted olefins. The results described in this paper contribute further development of the chemistry of magnesium carbenoid and also new synthesis of 2-alkenylated thiophenes.

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12. To a solution of **6** (98 mg; 0.3 mmol) in 6 mL of dry toluene in a flame-dried flask at $-78\text{ }^{\circ}\text{C}$ under argon atmosphere was added *t*-BuMgCl (1.0 M solution in THF, 0.04 mL; 0.04 mmol) dropwise with stirring. After 10 min, *i*-PrMgCl (2.0 M solution in THF, 0.42 mL; 0.84 mmol) was added dropwise to the reaction mixture to give magnesium alkylidene carbenoid **7**. In another flask, *n*-BuLi (1.65 M solution in hexane, 0.6 mL; 0.99 mmol) was added dropwise to a solution of thiophene (0.072 mL; 0.9 mmol) in a mixture of 3 mL of dry toluene and 1 mL of THF at $-78\text{ }^{\circ}\text{C}$ under argon atmosphere to give 2-lithiothiophene. After 30 min, this solution was added to a solution of carbenoid **7** through a cannula. Temperature of the reaction mixture was gradually allowed to warm to $-10\text{ }^{\circ}\text{C}$. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with CHCl_3 . The organic layer was dried over MgSO_4 and concentrated in vacuo. The residue was purified by silica gel flash column chromatography to give **8a** (55 mg; 78%) as a colorless oil; IR (neat) 3104, 2949, 2881, 1648, 1432, 1120, 1082, 1034, 907, 761, 693 cm^{-1} ; ^1H NMR δ 1.76 (4H, dt, $J = 6.5, 5.5$ Hz), 2.42 (2H, t, $J = 6.6$ Hz), 2.70 (2H, t, $J = 6.6$ Hz), 3.99 (4H, s), 6.36 (1H, s), 6.89 (1H, d, $J = 3.4$ Hz), 6.97 (1H, dd, $J = 5.1, 3.5$ Hz), 7.19 (1H, d, $J = 5.1$ Hz). MS m/z (%) 236 (M^+ , 100), 207 (40), 192 (9), 191 (13), 174 (17), 163 (10), 149 (12), 135 (30), 121 (14). Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}$: M, 236.0869. Found: m/z 236.0864.
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gel flash column chromatography to give **10** (E = CH₃) (53.9 mg; 72%) as colorless crystals; mp 54–54.5 °C (AcOEt–hexane); IR (KBr) 2947, 2880, 1438, 1364, 1232, 1124, 1097, 1034, 900, 764, 693 cm⁻¹; ¹H NMR δ 1.64 (2H, t, *J* = 6.4 Hz), 1.76 (2H, t, *J* = 6.4 Hz), 2.04 (3H, s), 2.40 (2H, t, *J* = 6.8 Hz), 2.47 (2H, t, *J* = 6.8 Hz), 3.97 (4H, s), 6.75 (1H, dd, *J* = 3.6, 1.3 Hz), 6.96 (1H, dd, *J* = 5.0, 3.4 Hz), 7.20 (1H, dd, *J* = 5.1, 1.1 Hz). MS *m/z* (%) 250

(M⁺, 100), 235 (21), 221 (26), 205 (15), 191 (25), 173 (15), 163 (22), 149 (47), 135 (27), 121 (12), 99 (23). Calcd for C₁₄H₁₈O₂S: *M*, 250.1025. Found: *m/z* 250.1024. Anal. Calcd for C₁₄H₁₈O₂S: C, 67.13; H, 7.23; S, 12.78. Found: C, 67.17; H, 7.25; S, 12.81.

15. Structure of products **12c** and **12d** was determined with their NOESY spectrum.