Synthesis of Unsymmetrically and Highly Substituted Thiophenes Utilizing Regioselective Ring-expansion of *gem*-Dichlorocyclopropyl Ketones with Lawesson's Reagent

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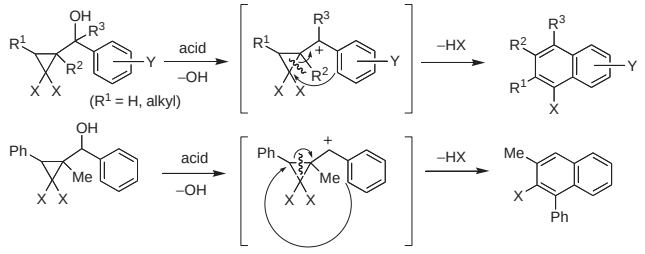
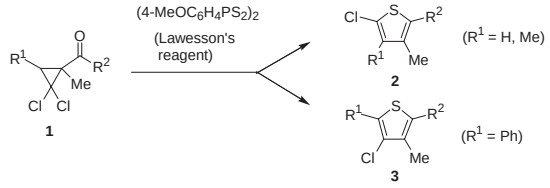
Ring-expansion of aryl *gem*-dichlorocyclopropyl ketones **1** using Lawesson's reagent afforded unsymmetrically and highly substituted 5-chloro and 3-chlorothiophenes **2** and **3** with excellent regioselectivity. The Suzuki–Miyaura coupling of **2** and **3** with $PhB(OH)_2$ was successfully performed to give 2-aryl-3-methyl-5-phenylthiophenes **4** and 2-aryl-3-methyl-4,5-diphenylthiophenes **5**, respectively.

Thiophene is a fundamental 5-membered heterocycle, commonly used as a building block in organic chemistry.[1] Highly substituted thiophenes have attracted considerable attention due to the recent production of useful synthetic intermediates for opto-electronic devices[2] and biologically active compounds.[3] Thus, there is a high demand for synthetic studies of thiophene derivatives.

Despite the demand, the synthesis of unsymmetrically and highly substituted thiophenes is quite limited. As a part of our ongoing program of synthetic studies on the transformation of *gem*-dihalocyclopropanes,[4–6] we previously reported a dual mode of highly regioselective benzannulation of *gem*-dichlorocyclopropylmethanols promoted by Lewis acids to afford α- and β-arylnaphthalenes (Scheme 1).[4a] To extend these findings, chirality-exchange[4c] and regiocontrolled[4d] benzannulations were recently presented. Here, we report a novel method for dual regioselective syntheses of unsymmetrically and highly substituted 5- and 3-chlorothiophenes **2** and **3** promoted by $(4\text{-MeOC}_6H_4PS_2)_2$ (Lawesson's reagent),[7] which involved a novel ring-expansion of *gem*-dichlorocyclopropyl ketones **1** (Scheme 2).

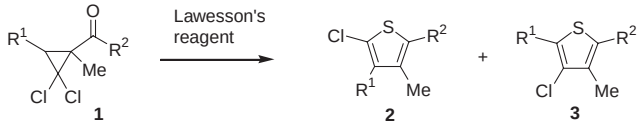


Scheme 1.



Scheme 2.

Table 1. Regioselective ring-expansion of *gem*-dichlorocyclopropanes **1** with Lawesson's reagent[a]



Entry	Substrate	R^1	R^2	Ratio of **2**/**3**	Product	Yield/%[b]
1	**1a**	H	Ph	>99/1	**2a**	51
2	**1b**	H	4-MeC_6H_4	>99/1	**2b**	60
3	**1c**	H	4-MeOC_6H_4	>99/1	**2c**	74
4	**1d**	Me	4-MeOC_6H_4	>99/1	**2d**	70
5	**1e**	Ph	Ph	<1/99	**3e**	75
6	**1f**	Ph	4-MeC_6H_4	<1/99	**3f**	67
7	**1g**	Ph	4-MeOC_6H_4	<1/99	**3g**	75
8	**1h**	Ph	2-MeOC_6H_4	<1/99	**3h**	74
9	**1i**	Ph	4-ClC_6H_4	<1/99	**3i**	69
10	**1j**	Ph	Me	<1/99	**3j**	53

[a]Carried out in chlorobenzene at 130 °C for 10 h. [b]Isolated.

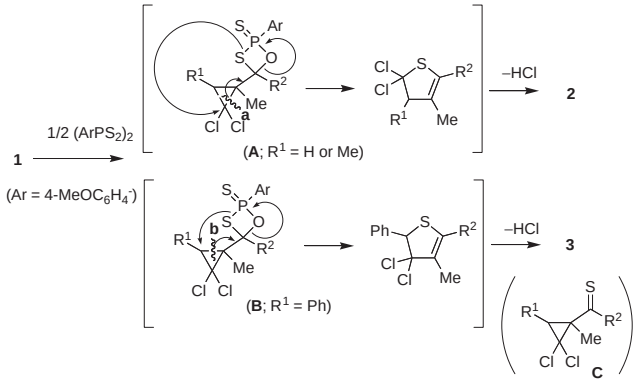
Application of this method to the synthesis of unsymmetrically and highly substituted thiophenes **4** and **5** was successfully performed utilizing the Suzuki–Miyaura coupling of **2** and **3** with $PhB(OH)_2$.

The initial attempt was guided by a reaction using ketone **1a** with Lawesson's reagent. A ring-expansion reaction unexpectedly occurred giving thiophene **2a** as the sole product in 51% yield (Table 1, Entry 1).[8] This result encouraged us to investigate the reaction using ketones **1b**–**1d** (R^1 = H or Me). The successful results are listed (Entries 2–4). In clear contrast, the reaction using ketones **1e**–**1j** (R^1 = Ph) gave regioisomeric thiophenes **3e**–**3j** in good yields, respectively. In every entry, some amounts of starting substrates **1** were recovered (18–30%). Notice that regioselectivity, including in the reaction using **1j** (R^2 = Me, Entry 10), was excellent in every case examined.

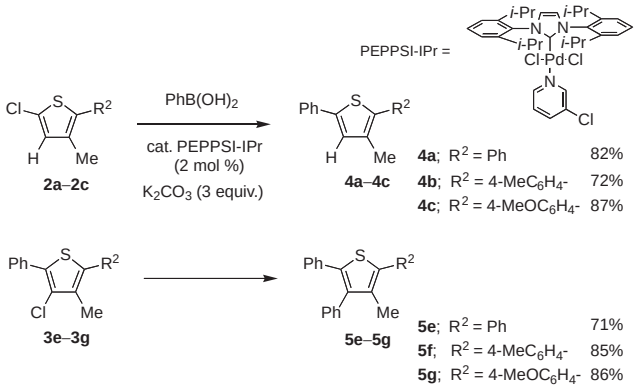
The proposed mechanism of the present reaction is depicted in Scheme 3. First, $(4\text{-MeOC}_6H_4PS_2)_2$ reacts with the carbonyl oxygen of **1** to give the oxathiaphosphetane intermediate **A** or **B**. Regioselective ring-expansion of **A** or **B** with the concomitant bond-cleavage (**a** or **b**) proceeds to give thiophenes **2** or **3**, accompanied by an oxygen–sulfur exchange and elimination of HCl.

This switching mode with regard to ring cleavage regioselectivity is consistent with the reported benzannulation (Scheme 1).[4a] Note that plausible transient thioketones **C** were not detected during the present reaction.

To demonstrate the utility of the present ring-expansion reaction, we planned the Suzuki–Miyaura coupling using chlorothiophenes **2** and **3** (Scheme 4). Compared with the popular re-



Scheme 3.



Scheme 4.

action using aryl chlorides with $PhB(OH)_2$, the present coupling proceed more smoothly due to the inherent higher reactivity of **2** and **3**. Thus, the recently improved method[9] using [1,3-di(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)-palladium(II) dichloride (PEPPSI-IPr) catalyst successfully afforded the desired 2-aryl-3-methyl-5-phenylthiophenes **4a**–**4c** and 2-aryl-3-methyl-4,5-diphenylthiophenes **5a**–**5c** in good yields.[10]

In conclusion, we developed a novel synthesis of substituted 5-chloro or 3-chlorothiophenes utilizing highly regioselective ring-expansion of *gem*-dichlorocyclopropyl ketones. As a further extension, the Suzuki–Miyaura coupling of these products was successfully performed to give unsymmetrically and highly substituted thiophenes. The present method provides a novel and facile access to such thiophene analogs.

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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 80th birthday.

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8 Typical procedure: A solution of *gem*-dichlorocyclopropyl ketone **1g** (340 mg, 1.0 mmol) and Lawesson's reagent (4-$MeOC_6H_4PS_2)_2$ (2.02 g, 5.0 mmol) in chlorobenzene (12.5 mL) was stirred at 130 °C for 10 h under an argon atmosphere. Water was added to the reaction mixture, which was extracted with ether. The organic phase was washed with sat. $NaHCO_3$ aqueous solution, brine, dried (Na_2SO_4), and concentrated to give crude oil. The obtained crude product was purified by silica-gel column chromatography (hexane) to give thiophene **3g** (236 mg, 75%): Colorless crystal; mp 63–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 3.84 (s, 3H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 55.3, 114.1, 126.3, 127.6, 128.3, 129.9, 130.5, 131.7, 134.9, 135.2, 140.7, 159.2; IR ($CHCl_3$) 3058, 2835, 1515, 1033, 829 cm^{-1}, HRMS (EI, m/z): M^+ calcd for $C_{19}H_5ClOS$ 314.0532, found 314.0526.

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10 Typical procedure: K_2CO_3 (150 mg, 1.1 mmol) was added to a solution of PEPPSI-IPr catalyst (5 mg, 0.007 mmol), thiophene **2a** (50 mg, 0.24 mmol), and $PhB(OH)_2$ (44 mg, 0.36 mmol) in dioxane (2.0 mL). The mixture was stirred at 60 °C for 4 h under an argon atmosphere. Then, the mixture was concentrated to give crude oil, which was purified by silica-gel column chromatography (hexane) to give thiophene **4a** (49 mg, 82%). Colorless crystals; mp 86–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 7.14 (s, 1H), 7.34 (m, 6H), 7.50 (m, 2H), 7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 125.5, 127.2, 127.2, 127.3, 128.5, 128.8, 128.8, 134.1, 134.3, 134.7, 137.4, 141.8; IR ($CHCl_3$) 3018, 1598, 1488, 1215, 756 cm^{-1}. The use of conventional catalyst, $Pd(PPh_3)_4$, under the identical conditions resulted in less yield (10%).

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