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CONSTRUCTION OF FUSED THIOPHENE RING SYSTEM *VIA* INTRAMOLECULAR CH ARYLATION BY PALLADIUM CATALYSIS[‡]

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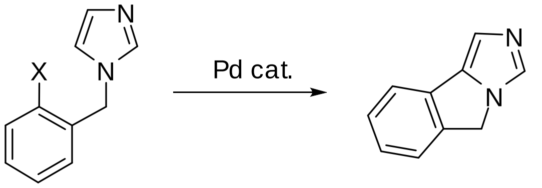
[‡]This paper is dedicated to Professor Akira Suzuki, who made great contribution to cross coupling chemistry, on the occasion of his 80th birthday.

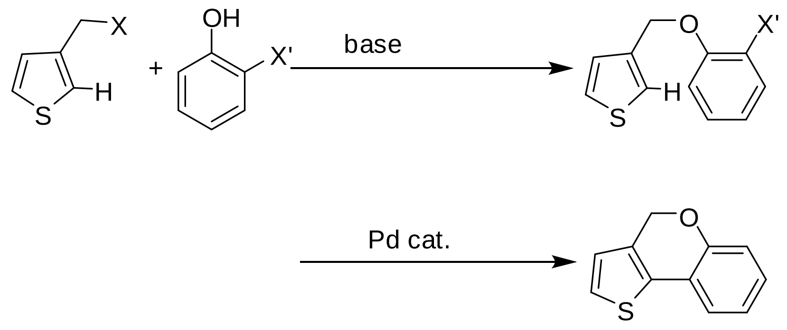
Abstract – Intramolecular CH arylation of a thiophene derivative in the presence of a palladium catalyst furnishes fused tricyclic thiophene in a high yield. The obtained thiophene undergoes further intermolecular CH arylation with a palladium catalyst and $AgNO_3$/KF.

A transition metal-catalyzed coupling reaction to form a carbon–carbon bond is an important tool in organic synthesis to construct the skeleton of a complex organic molecule.[1] The coupling reaction at a carbon–hydrogen bond is a recent concern[2-4] due to its high atom efficiency compared to that with the use of the related organometallic reagents. The intramolecular version of such coupling reactions are of particular interest since the reaction allows construction of the corresponding ring system. We have recently shown that a five-membered nitrogen heteroaromatic compound undergoes intramolecular CH arylation in the presence of a palladium catalyst.[5] (eq 1) The obtained product possesses the tricyclic heteroaromatic ring structure, where the heterocycle is fused at the carbon–nitrogen bond.



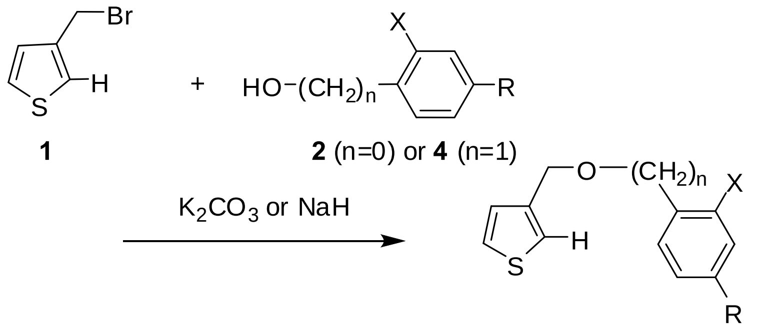
(1)

Our further concern is focused on the development of a synthetic protocol for other ring systems fused by a carbon–carbon bond and/or bearing a different heteroatom. Herein, we report a palladium-catalyzed intramolecular CH arylation of thiophene derivatives leading to sulfur-containing tricyclic compounds, where the ring system on the thiophene ring is fused by a carbon–carbon bond[6] (Scheme 1).



Scheme 1

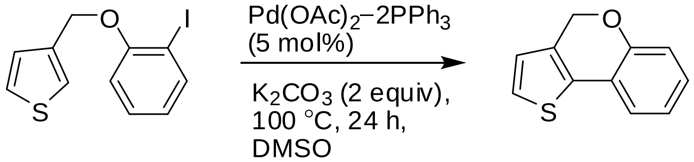
Synthesis of the precursor for tricyclic thiophene was carried out as summarized in Scheme 2. The reaction of 3-bromomethyl-thiophene (**1**, X=Br) with phenol derivative **2** proceeded smoothly in the presence of potassium carbonate to obtain the corresponding ether **3** in 42 to 97% yields. The reaction of **1** with benzylic alcohol **4** also took place to afford **5** (54%) when NaH was employed as a base.



3a	R=H	X=I	n=0	97%
3a'	R=H	X=Br	n=0	42%
3b	R=^{t}Bu	X=I	n=0	77%
3c	R=NO_2	X=I	n=0	67%
5	R=H	X=I	n=1	54%

Scheme 2

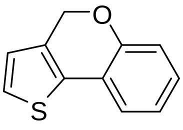
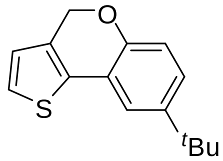
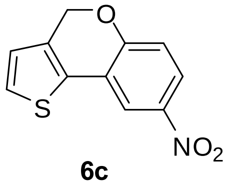
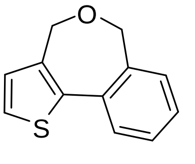
First, we examined the palladium-catalyzed CH arylation reaction with $AgNO_3$/KF as an activator under similar conditions to the intermolecular version that we reported previously,[4d] however, the reaction was unsuccessful to result in giving unidentified undesired side products. Uncontrolled intra- and intermolecular CH arylation as well as CH homocoupling would occur at the CH bond of 2- and 5-positions of the thiophene ring leading to the formation of a complex mixture of oligomers. By contrast, the use of potassium carbonate as an additive[3a] underwent the intramolecular CH arylation smoothly at the 2-position of thiophene to afford the corresponding tricyclic product in 92% yield.



3a **6a** (92%)

Several ether derivatives **3** were similarly subjected to the palladium-catalyzed reactions in the presence of potassium carbonate as an additive to obtain the corresponding tricyclic thiophene derivatives in excellent yields. The reaction of aryl bromide **3a'** also proceeded although the yield of **6a** was slightly inferior. The reaction of the benzylic ether derivative **5** to cause ring closure forming the seven-membered ring also proceeded smoothly to afford **7** in 92% yield. The results are summarized in Table 1.

Table 1. Intramolecular CH arylation of thiophene derivatives[a]

Substrate	Product	%yield
3a	 **6a**	92
3a'	**6a**	57
3b	 **6b**	54
3c	 **6c**	97
5	 **7**	92

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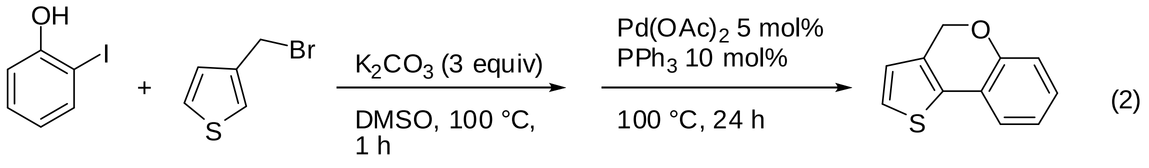
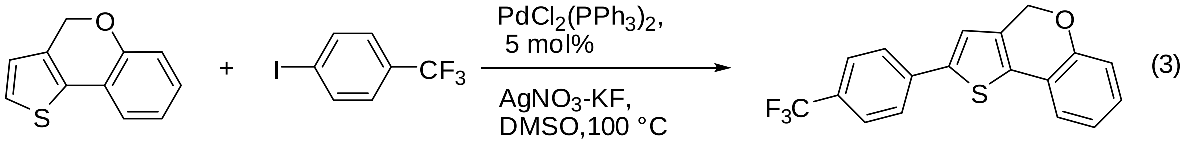
[a] The reaction was carried out using **3** or **5** (0.5 mmol), K_2CO_3 (1.0 mmol), $Pd(OAc)_2$ (10 mol%), and PPh_3 (20 mol%) in 3 mL of DMSO under argon atmosphere at 100 ºC for 24 h.

It was found that one-pot synthesis of the tricyclic ring system was also successful by the reaction of 3-(bromomethyl)thiophene (**1**) and iodophenol (**2a**). Treatment of **1** and **2a** with potassium carbonate at 100 ºC for 1 h and following addition of the palladium catalyst system (10 mol%) afforded **6a** in 82% yield.



1 **6a** 82%

Since the product obtained by the intramolecular CH arylation **6** and **7** still possesses a reactive CH bond toward the direct arylation on the thiophene ring, further intermolecular arylation reaction would be possible. The CH arylation of **6a** with $AgNO_3$/KF system, which we have shown previously,[4d] was conducted. The corresponding coupling product **8** was obtained in 40% yield when 4-iodo-benzotrifluoride was employed. (eq 3) The obtained **8** would be potentially applicable for various organic materials. Further studies concerning spectroscopic characterization, measurement of electrochemical and thermal (liquid crystalline) properties of several highly substituted fused thiophene derivatives will be described in due course.



6a **8**, 40%

In conclusion, we showed that intramolecular CH arylation on the thiophene ring took place smoothly by the catalysis of palladium leading to form a fused tricyclic thiophene derivatives. The reaction precursors were easily synthesized by the Williamson ether synthesis with halomethyl-thiophene and phenol (benzylic alcohol). The synthetic method allows to afford variety of fused thiophenes and extends a library of thiophene derivatives for the design of biologically active and/or advanced organic materials.[7]

ACKNOWLEDGEMENT

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7. Typical experimental procedure: To a 25 mL of Schlenk tube equipped with a magnetic stirring bar were added K_2CO_3 (135.2 mg, 1.0 mmol), DMSO (3.0 mL), **3c** (180.6 mg, 0.50 mmol), Pd(OAc)$_2$ (5.6 mg, 0.025 mmol), and triphenylphosphine (13.1 mg, 0.050 mmol) under N_2. The resulting

mixture was heated at 100 °C for 24 h. After cooling to room temperature the mixture was diluted with 20 mL of ethyl acetate and passed through a Celite pad. The cake was washed with 10 mL of ethyl acetate. The filtrate was washed with 20 mL of water. The aqueous phase was extracted with ethyl acetate twice. The organic layer was washed twice with water and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left a crude solid, which was purified by chromatography on silica gel to afford 113.1 mg of **6c**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.47 (1H, s), 6.86 (1H, d, J = 5.4 Hz), 6.97 (1H, d, J = 8.7 Hz), 7.37 (1H, d, J = 5.4 Hz), 8.03 (1H, d, J = 8.7 Hz), 8.17 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.4, 116.6, 118.2, 120.0, 124.0, 124.2, 129.8, 131.7, 142.0, 156.9; IR (KBr) 1590, 1490, 1339, 1328, 1266, 1092, 993, 886, 728 cm^{-1}; HRMS(EI, *m*/*z*) Calcd for $C_{11}H_7NO_3S$: 233.0147. Found: 233.0146.