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Selectively Substituted Thiophenes and Indoles by a Tandem Palladium-Catalyzed Multicomponent Reaction

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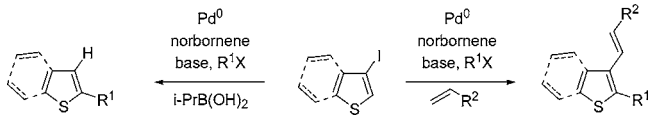
ABSTRACT



A variety of di- and trisubstituted thiophenes were synthesized by a one-pot palladium-catalyzed ortho-alkylation sequence terminated by either Heck or C–H coupling. Initial results toward the functionalization of indoles are also presented.

Polysubstituted thiophenes are useful compounds for both pharmaceutical[1] and material sciences.[2] While a number of methods have been reported for their preparation, selective substitution remains as a challenging goal.[1,5] Various sequential substitution reactions have been reported for aromatic compounds, most notably using palladium catalysis;[3,4] however, there are few reports in this area pertaining to thiophenes.[5] We are interested in the sequential substitution of aromatic compounds and recently reported a method for the formation of fused aromatic rings[6] based on the work of Catellani and co-workers.[7]

We have extended the ortho-alkylation procedure to include heteroaryl halides and now report a route to selectively functionalized thiophenes.

Initial studies found that 2-iodothiophene is a poor substrate for the tandem ortho-alkylation/Heck coupling reaction. Thus, we examined commercially available 3-iodothiophene (**1**) as a substrate (Table 1). Among several parameters tested, $Pd(OAc)_2$ and tri-2-furylphosphine (TFP) in CH_3CN gave the best yield of the desired product **2a** compared to the direct Heck product **3**.[8,9] The amount of norbornene greatly affects the yield of **2a**, improving with

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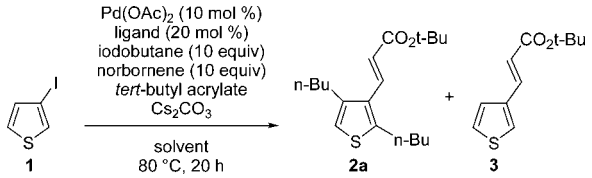
Table 1. Optimization of Domino Alkylation/Heck Reaction



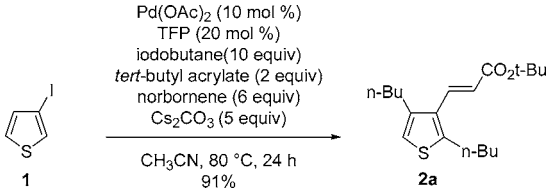
entry	solvent	ligand	*tert*-butyl acrylate (equiv)	Cs_2CO_3 (equiv)	yield[a] (%) **2a**	**3**
1[b]	DME	PPh_3	5	2	<1	46
2[b]	DME	TFP	5	2	<1	43
3[b]	Dioxane	TFP	5	2	<1	59
4[b]	CH_3CN	TFP	5	2	<1	56
5	CH_3CN	TFP	5	2	37	26
6	DME	PPh_3	2	5	75	0
7	DME	TFP	2	5	69	0
8	CH_3CN	TFP	2	5	80	0
9	CH_3CN	PPh_3	2	5	56	0

[a] Isolated yields. [b] With 2 equiv of norbornene.

increasing equivalents of norbornene and reaching a maximum at 6 equivalents.

The optimal conditions of **1** (1.0 equiv), 1-iodobutane (10 equiv), and *tert*-butyl acrylate (2.0 equiv) at 80 °C in CH_3CN in the presence of $Pd(OAc)_2$ (10 mol %), TFP (20 mol %), norbornene (6.0 equiv), and Cs_2CO_3 (5.0 equiv) gave the trisubstituted product **2a** in 91% yield (Scheme 1). The use of 3-bromothiophene under the same reaction conditions gave **2a** in 33% yield.

Scheme 1. Optimal Conditions for the Domino Ortho-Alkylation/Heck Coupling Reaction



The proposed mechanism is presented in Scheme 2.[7,10]

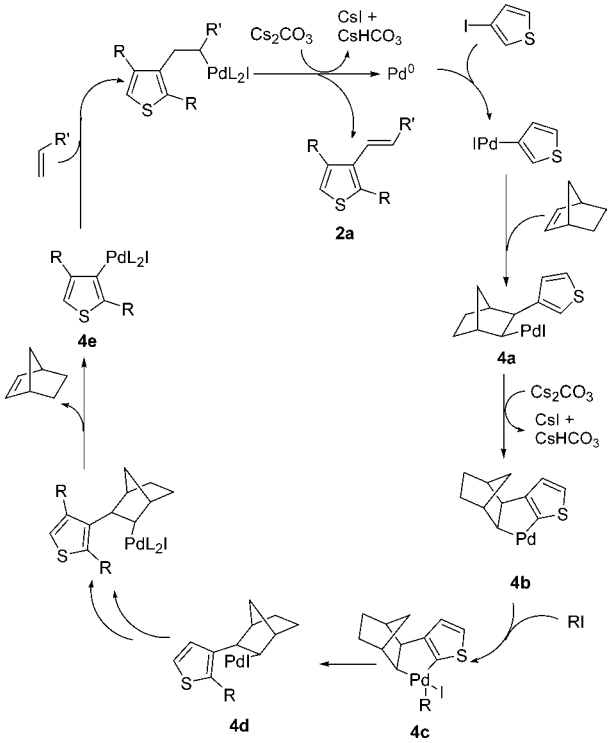
Pd(0) inserts into the C−I bond of 3-iodothiophene, followed by carbopalladation of norbornene to give **4a**. C−H activation of the 2-position forms **4b**. Oxidative addition of the alkyl iodide leads to the Pd(IV) species **4c** and reductive elimination generates **4d**. This process then occurs for the 4-position C−H bond, and extrusion of norbornene gives the 2,4-dialkylated 3-(thienyl)palladium(II) complex **4e**.

(8) The use of $Pd(OAc)_2$ as a palladium source gave the best selectivity. The reaction using $Pd_2(dba)_3{\cdot}CHCl_3$ or $PdCl_2(CH_3CN)_2$ as a catalyst precursor gave the direct Heck product as the major product together with trace amounts of the desired compound.

(9) The use of PPh_3 also gives **2a** in comparable but lower yields.

(10) This mechanism is based on mechanistic studies of Catellani, Pregosin, and co-workers (ref 6c,d) and on our own preliminary studies.

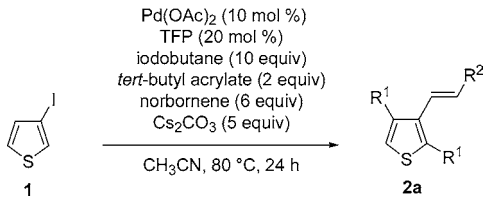
Scheme 2. Proposed Mechanism



Alternatively, C−H activation of the 4-position could take place in the first step; however, at this time we do not know which C−H activation occurs first. Heck reaction with **4e** yields product **2a**. We believe an excess of norbornene is needed to compete with the direct Heck pathway.

The scope of this reaction is presented in Table 2.[11] In all cases, trisubstituted products were obtained in moderate to high yields. In addition to *tert*-butyl acrylate, ethyl and

Table 2. Scope of the Ortho-Alkylation/Heck Coupling

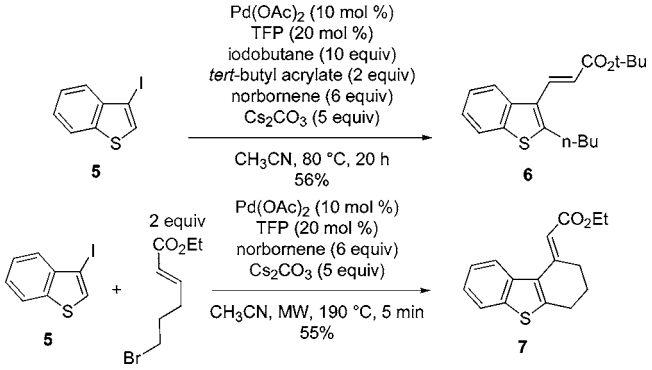


entry	R^1	R^2	**2** (yield, %)[a]
1	*n*-Bu	CO_2-*t*-Bu	**2a** (91)
2	*n*-Bu	CO_2Et	**2b** (96)
3	*n*-Bu	CO_2Me	**2c** (65)[b]
4	*n*-Bu	$C(O)NMe_2$	**2d** (70)[c]
5	*n*-Bu	C(O)NH-*t*-Bu	**2e** (54)[b]
6	*n*-Bu	C(O)Et	**2f** (52)
7	$TBSO(CH_2)_3$	CO_2Et	**2g** (74)
8	$Ph(CH_2)_3$	CO_2Et	**2h** (82)[b]
9	$Cl(CH_2)_3$	CO_2-*t*-Bu	**2i** (55)[c]

[a] Isolated yields. [b] With 4 equiv of norbornene. [c] With 10 equiv of norbornene.

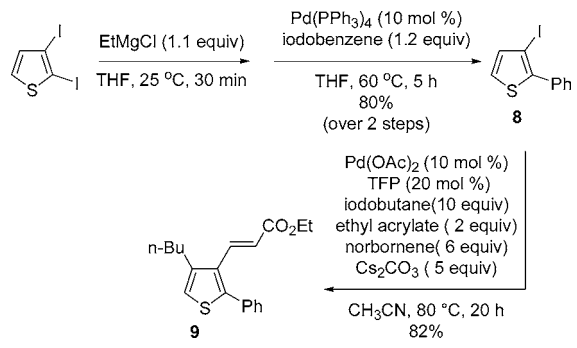
methyl acrylate can be used as Heck acceptors (entries 1−3), as well as acrylamides (entries 4−5) and ethylvinyl ketone (entry 6). A variety of iodides with remote reactive functional groups were also tolerated under the reaction conditions (entries 7−9). The ortho-alkylation/Heck coupling reaction was further extended to 3-iodobenzo[*b*]thiophene (**5**) to give the adduct **6** in 56% yield. Using a bis-acceptor produced tricyclic compound **7** in 55% yield (Scheme 3). To the best of our knowledge, these are the first examples of Heck reactions using 3-iodobenzo[*b*]thiophenes.

Scheme 3. Ortho-Alkylation/Heck Couplings Using **5**



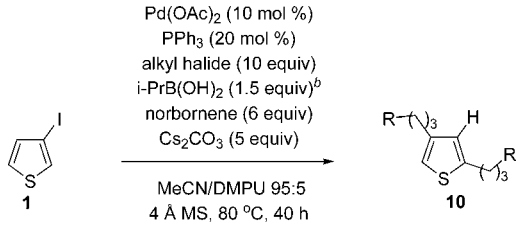
To create an unsymmetrically substituted thiophene at the 2- and 4-positions, regioselective halogen−magnesium exchange[12] of 2,3-diiodothiophene with EtMgCl (1.1 equiv) produced the 2-substituted Grignard reagent,[13] which underwent Kumada−Tamao−Corriu coupling[14] with iodobenzene (1.2 equiv) and $Pd(PPh_3)_4$ (10 mol %) to give **8** in 80% yield (Scheme 4). Subjecting **8** to our optimized conditions gave unsymmetrically substituted thiophene **9** in 82% yield.

Scheme 4. Use of 2,3-Diiodothiophene



To generate 2,4-disubstituted thiophenes, an ortho-alkylation/C−H coupling previously developed in our group for iodoarenes[15] was applied to 3-iodothiophene to produce **10** (Table 3). Compared to arenes, lower temperatures and longer reaction times were needed to inhibit thiophene polymerization and decomposition. The mechanism for this transformation is similar to Scheme 2, although the terminating step from **4e** is a C−H coupling using isopropylboronic acid. Though the yields are moderate to low, a variety of functional groups are tolerated, and afford products which are difficult to synthesize using classical methods. The functionalized alkyl chains can also be useful synthetic handles for further modification.

Table 3. Scope of Ortho-Alkylation/C−H Coupling

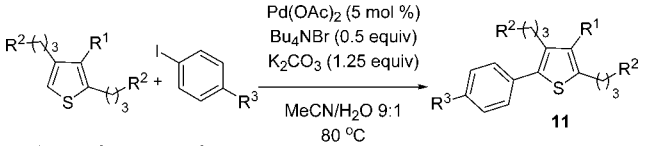


entry	R	yield[a] (%)
1	CO_2Et	**10a** (42)
2	1-oxirane	**10b** (54)
3	2-(1,3)-dioxolane	**10c** (36)
4	*N*-phthalimide	**10d** (24)
5	CN	**10e** (26)

[a] Isolated yields. [b] Slow addition.

To create tri- and tetrasubstituted thiophenes, the 5-position was functionalized using direct thiophene arylation[16] to generate a 2,4,5-trisubstituted thiophene (**11a**) and tetrasubstituted thiophenes (**11b** and **11c**) (Scheme 5) in good yields from the parent compounds.

Scheme 5. Direct Thiophene Arylation of Selectively Substituted Thiophenes

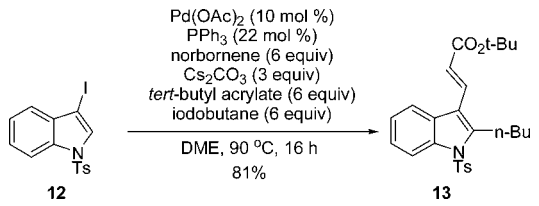


R^1 = H, R^2 = CO_2Et, R^3 = NO_2 (**11a**, 64%)
R^1 = CH=CHCO_2t-Bu, R^2 = CH_3, R^3 = NO_2 (**11b**, 68%)
R^1= CH=CHCO_2t-Bu, R^2 = CH_3, R^3 = OMe (**11c**, 62%)

Our next goal was to extend the methodology to the functionalization of indoles, a structural motif that is very common in a number of natural products and medicinally important compounds. After careful screening of the reaction parameters, we were able to achieve 81% yield of the desired

(11) Typical procedure for sequential alkylation/alkenylation reaction of 3-iodothiophene (Table 2, entry 1): A mixture of 3-iodothiophene (42 mg, 0.2 mmol), 1-iodobutane (368 mg, 2.0 mmol), *tert*-butyl acrylate (53 mg 0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol %), TFP (9.3 mg, 20 mol %), norbornene (113 mg, 1.2 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in dry CH_3CN (2.0 mL) was stirred at 80 °C for 20 h under nitrogen. After being cooled to room temperature, the resulting mixture was treated with water and extracted with Et_2O. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/AcOEt = 20/1−10/1) to afford **2a** (59 mg, 91%) as a pale yellow oil.

Scheme 6. Optimized Coupling for 2,3 Coupling of 3-Iodoindole



product **13** (Scheme 6). Fortuitously, it could be crystallized which provided a method to unquivocally prove the structure of **13**. During the course of optimization, it was found that the nature of the nitrogen protecting group was crucial to the efficiency of the reaction. Use of a methyl protecting group yielded only the direct Heck product.

In summary, we have established a palladium-catalyzed tandem alkylation/alkenylation reaction of 3-iodothiophene to construct trisubstituted thiophenes in good yields. In addition, 3-iodobenzo[*b*]thiophene and 2-substituted 3-iodothiophene can be used. Application of our ortho-alkylation/C−H coupling produces 2,4-disubstituted thiophenes, and direct arylation of di- and trisubstituted thiophenes produces 2,4,5-trisubstituted and tetrasubstituted thiophene derivatives. Finally, this methodology has also been extended to include indoles, the scope of which is currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Knochel and co-workers reported that polyfunctional arylmagnesium and alkenylmagnesium reagents can be prepared by iodine−magnesium exchange reaction: Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *36*, 4302−4320 and references therein.

(13) Regioselective halogen−magnesium exchange reaction of 2,3-dibromothiophene was reported; see: Christophersen, C.; Begtrup, M.; Ebdrup, S.; Petersen, H.; Vedsø, P. *J. Org. Chem.* **2003**, *68*, 9513−9516.

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