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Palladium-Catalyzed Direct Arylation of Free NH_2-Substituted Thiophene Derivatives

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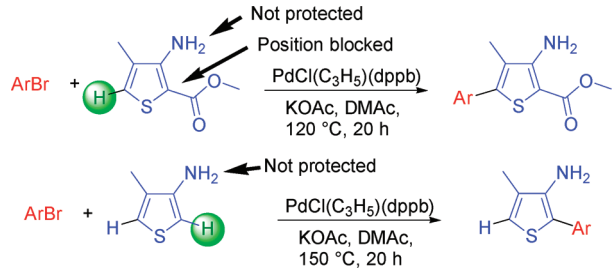
ABSTRACT



The palladium-catalyzed direct 2- or 5-arylation of some free NH_2-substituted thiophene derivatives was found to proceed in high yields using a variety of aryl bromides. In the course of these reactions, no coupling of the aryl bromide with the thiophene NH_2 substituent was detected. The presence of an ester substituent on C2 of thiophene was found to be useful to block this highly reactive carbon.

In recent years, the palladium-catalyzed direct arylation of heteroaromatics has emerged as a very powerful method for the preparation of arylated thiophenes.[1−3] However, there are still limitations for these reactions in terms of heteroaromatic functional group tolerance. If the presence of acetyl, formyl, nitrile, and methylalcohol as the functional groups on the thiophenes has been described,[4] on the other hand, the use of free NH_2 substituents has attracted much less attention.[5,6] In a few cases, protected amines have been employed.[7−10] However, the direct use of heteroaromatics bearing unprotected functions, such as NH_2, would be more useful in organic synthesis since it would allow us to avoid the protection/deprotection sequence and would provide a more environmentally and economically attractive access to such arylated heteroaromatics.[8,9] Therefore, the discovery of effective conditions, for the direct coupling of such aminothiophenes with aryl halides, would be a considerable advantage for industrial applications and for sustainable development. Here, we wish to report on the reaction of

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(1) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Doucet, H.; Hierso, J. C. *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 672. (d) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (g) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (h) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (i) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.

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(3) For selected recent examples of direct arylations of thiophenes: (a) Fournier Dit Chabert, J.; Chatelain, G.; Pellet-Rostaing, S.; Bouchu, D.; Lemaire, M. *Tetrahedron Lett.* **2006**, *47*, 1015. (b) Nakano, M.; Satoh, T.; Miura, M. *J. Org. Chem.* **2006**, *71*, 8309. (c) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999. (d) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (e) Amaladass, P.; Clement, J. A.; Mohanakrishnan, A. K. *Tetrahedron* **2007**, *63*, 10363. (f) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851.

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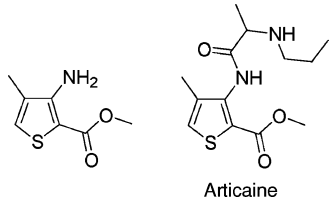


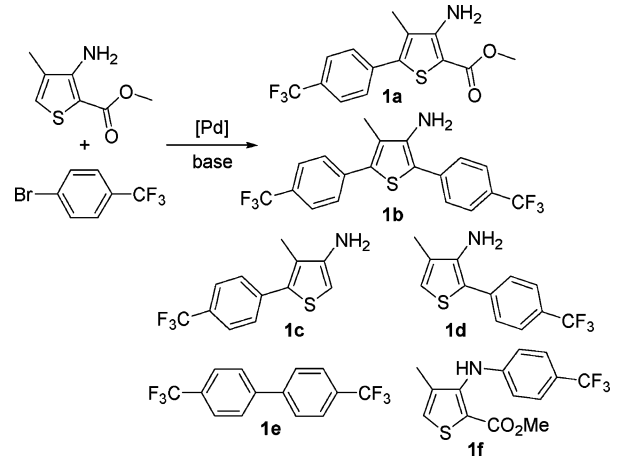
Figure 1. Articaine and its precursor.

thiophene derivatives bearing unprotected amino functions with a set of electronically and sterically diverse aryl bromides.

We decided to employ methyl 3-amino-4-methylthiophene-2-carboxylate as the test substrate for our study. Carbon C2 of this substrate is blocked by an ester which can be easily removed. This commercially available compound is a precursor of articaine (Figure 1), which is actually the most widely used local dental anesthetic in several European countries.

First, we examined the influence of the base, solvent, catalyst precursor, and reaction temperature for the coupling of 4-(trifluoromethyl)bromobenzene with methyl 3-amino-4-methylthiophene-2-carboxylate (Scheme 1, Table 1). We observed that, in the course of this reaction, several compounds can be obtained. However, the amination product **1f** was not detected. On the other hand, the 2,5-diarylated product **1b** and the decarboxylated product **1c** were obtained in relatively high yields in some cases. We initially examined the influence of the nature of the base on the product distribution for this reaction using DMAc as the solvent. DMAc is known to be a good solvent for direct arylations of heteroaromatics.[4j] K_2CO_3, Na_2CO_3, or Cs_2CO_3 gave poor conversions of 4-(trifluoromethyl)bromobenzene, and target

Scheme 1



compound **1a** was obtained only in traces (Table 1, entries 1−3). The use of acetates as the base gave better results, and the desired compound **1a** was obtained in 19−43% selectivity together with moderate to large amounts of **1b** and **1c** (Table 1, entries 4−6). It should be noted that the inter- or intramolecular palladium-catalyzed amination of some 3-aminothiophenes with aryl bromides has been described using Cs_2CO_3 or K_3PO_4 as the bases in toluene.[11] Interestingly, acetate appears to not be suitable to catalyze the amination reaction, as no trace of **1f** was detected. The good performance of acetates as the bases is consistent with a concerted metalation deprotonation (CMD) pathway.[4k] Then, to reduce the amount of decarboxylated products, we performed the reaction at 120 °C instead of 150 °C. At this temperature, in the presence of KOAc as the base, DMAc

Table 1. Influence of the Reaction Conditions on the Selectivity for the Arylation of Methyl 3-Amino-4-methylthiophene-2-carboxylate with 4-(Trifluoromethyl)bromobenzene (Scheme 1)[a]

entry	solvent	base	catalyst	temp (°c)	convn (%)	ratio **1a**:**1b**:**1c**:**1e**
1	DMAc	K_2CO_3	$PdCl(C_3H_5)(dppb)$	150	5	–
2	DMAc	Na_2CO_3	$PdCl(C_3H_5)(dppb)$	150	13	2:0:1:8
3	DMAc	Cs_2CO_3	$PdCl(C_3H_5)(dppb)$	150	11	2:1:4:0
4	DMAc	CsOAc	$PdCl(C_3H_5)(dppb)$	150	98	43:37:12:2
5	DMAc	NaOAc	$PdCl(C_3H_5)(dppb)$	150	43	28:5:5:4
6	DMAc	KOAc	$PdCl(C_3H_5)(dppb)$	150	100	19:66:11:3
7	DMAc	KOAc	$PdCl(C_3H_5)(dppb)$	120	100	93:3:1:1[b]
8	NMP	KOAc	$PdCl(C_3H_5)(dppb)$	120	100	84:2:3:10
9	DMF	KOAc	$PdCl(C_3H_5)(dppb)$	120	93	84:4:0:5
10	toluene	KOAc	$PdCl(C_3H_5)(dppb)$	120	63	58:0:0:5
11	DMAc	KOAc	$Pd(OAc)_2$[c]	120	100	78:15:6:1
12	DMAc	KOAc	$Pd(OAc)_2$/dppb	120	92	83:1:0:8
13	DMAc	KOAc	1/2 $[PdCl(C_3H_5)]_2$	120	100	78:0:6:9
14	DMAc	KOAc	1/2 $[PdCl(C_3H_5)]_2$/dppe	120	100	92:1:1:6
15	DMAc	KOAc	1/2 $[PdCl(C_3H_5)]_2$/2 PPh_3	120	83	75:2:0:5

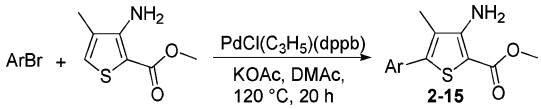
[a] Conditions: [Pd] (0.02 equiv), 4-(trifluoromethyl)bromobenzene (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), base (2 equiv), 20 h. Conversion of 4-(trifluoromethyl)bromobenzene. Traces of 4-(trifluoromethyl)benzene were also observed in some cases. [b] **1a** was isolated in 82% yield. [c] $Pd(OAc)_2$, 0.01 equiv.

as the solvent, and $PdCl(C_3H_5)(dppb)$ as the catalyst, **1a** was obtained in 82% yield (Table 1, entry 7).

Quite similar results were obtained in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) as the ligand, whereas the use of PPh_3 led to a lower conversion of the aryl bromide (Table 1, entries 14 and 15).

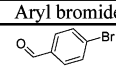
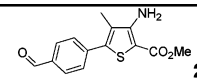
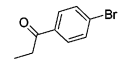
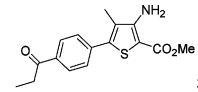
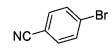
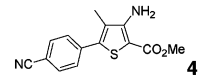
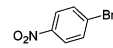
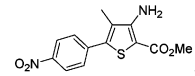
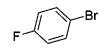
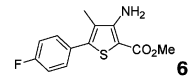
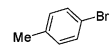
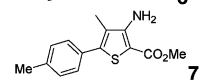
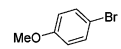
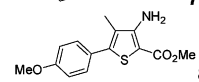
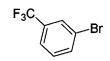
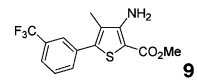
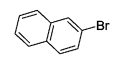
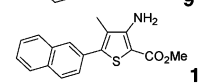
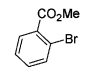
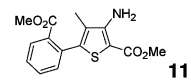
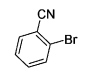
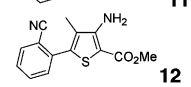
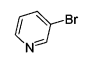
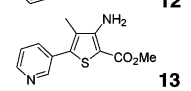
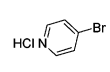
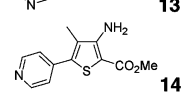
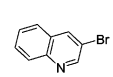
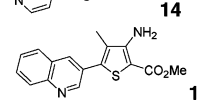
Then, methyl 3-amino-4-methylthiophene-2-carboxylate was coupled to a set of aryl bromides (Scheme 2, Table 2).

Scheme 2



The reactions performed with *para*-substituted electron-deficient aryl bromides proceed conveniently. Selective 5-arylations were observed using 4-bromobenzaldehyde, 4-bromopropiophenone, 4-bromobenzonitrile, 4-bromonitrobenzene, or 4-bromofluorobenzene, resulting in 83−89% yields of the products **2**−**6** (Table 2, entries 1−5). Electron-rich aryl bromide, 4-bromoanisole, gave **8** in a lower yield of 58% due to a partial conversion (Table 2, entry 7). As expected, the *meta*-substituted aryl bromide, 3-(trifluoromethyl)bromobenzene gave **9** in very high yield (Table 2, entry 9). Congested substrates, such as methyl 2-bromobenzoate or 2-bromobenzonitrile, were also found to be reactive under these reaction conditions and gave **11** and **12** in 87 and 90% yields, respectively (Table 2, entries 10 and 11).

Table 2. Direct Arylation of Methyl 3-Amino-4-methylthiophene-2-carboxylate (Scheme 2)[b]

Entry	Aryl bromide	Product	Yield (%)
1		 **2**	87
2		 **3**	86
3		 **4**	87
4		 **5**	83
5		 **6**	89
6		 **7**	81
7		 **8**	58
8		 **9**	92
9		 **10**	80
10		 **11**	87
11		 **12**	90
12		 **13**	77
13		 **14**	89[a]
14		 **15**	70

[a] KOAc, 3 equiv. [b] Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), KOAc (2 equiv), DMAc, 20 h, 120 °C.

Pyridines are probably the most common heterocyclic motif found in pharmaceutically active compounds. Therefore, preparative methods of biheteroaryl derivatives containing pyridines remain an essential research topic in organic synthesis. We observed that the coupling of 3- or 4-bromopyridines or 3-bromoquinoline with methyl 3-amino-4-methylthiophene-2-carboxylate also proceeds nicely to give **13**−**15** in good yields (Table 2, entries 12−14).

As the decarboxylation of methyl 3-amino-4-methylthiophene-2-carboxylate in the presence of a relatively strong base is quite easy, we examined the reactivity of this substrate using

(4) For examples of palladium-catalyzed direct arylations using thiophenes bearing formyl-, acetyl-, nitrile-, halo-, or methylalcohol substituents: (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (b) Lavenot, L.; Gozzi, C.; Ilg, K.; Orlova, I.; Penalva, V.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 49. (c) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (d) Hassan, J.; Gozzi, C.; Schulz, E.; Lemaire, M. *J. Organomet. Chem.* **2003**, *687*, 280. (e) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (f) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083. (g) Kobayashi, K.; Mohamed Ahmed, M. S.; Mori, A. *Tetrahedron* **2006**, *62*, 9548. (h) Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Adv. Synth. Catal.* **2007**, *349*, 2507. (i) Derridj, F.; Gottumukkala, A. L.; Djebbar, S.; Doucet, H. *Eur. J. Inorg. Chem.* **2008**, 2550. (j) Roger, J.; Pozğan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 425. (k) Liégaut, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (l) Dong, J. J.; Roger, J.; Doucet, H. *Tetrahedron Lett.* **2009**, *50*, 2778. (m) Roger, J.; Požgan, F.; Doucet, H. *Adv. Synth. Catal.* **2010**, *352*, 696. (n) Liégault, B.; Petrov, I.; Gorlesky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

(5) For examples of palladium-catalyzed direct arylations using free-(NH_2) adenines: Sahnoun, S.; Messaoudi, S.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2008**, *49*, 7279.

(6) For intramolecular cyclizations of aniline derivatives: Ackermann, L.; Althammer, A.; Mayer, P. *Synthesis* **2009**, 3493.

(7) For examples of palladium-catalyzed direct arylations using protected 2-aminothiazoles: (a) Priego, J.; Gutierrez, S.; Ferritto, R.; Broughton, H. B. *Synlett* **2007**, 2957. (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.

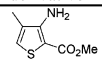
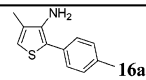
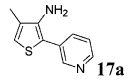
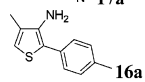
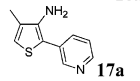
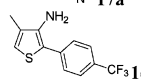
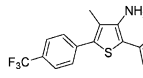
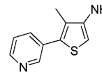
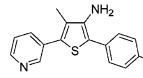
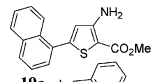
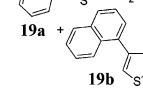
(8) For an example of palladium-catalyzed intramolecular direct arylations using a protected 2-aminofuran: Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716.

(9) For examples of palladium-catalyzed direct arylations using protected 2- or 3-aminothiophenes: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Synthesis* **2008**, 136. (b) Roger, J.; Doucet, H. *Eur. J. Org. Chem.* **2010**, 4412.

(10) For an example of palladium-catalyzed intramolecular direct arylation using an aminothiophene derivative: Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 3737.

(11) (a) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Tetrahedron* **2006**, *62*, 11100. (b) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Tetrahedron* **2007**, *63*, 690.

Table 3. Direct Arylations of Aminothiophene Derivatives[e]

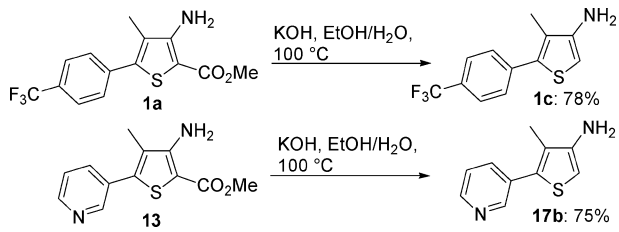
Entry	Thiophene derivative	Aryl bromide	Product	Yield (%)
1			 **16a**	64[a]
2			 **17a**	66[a]
3			 **16a**	79[b]
4			 **17a**	78[b]
5			 **1d**	77[b]
6			 **1b**	70[c]
7	 **17b**		 **18**	75[b]
8			 **19a** +  **19b**	52[b,d] (**19a**) + 12 (**19b**)

[a] KOH, 1.5 equiv was added. [b] KOAc (2 equiv). [c] Aryl bromide (2 equiv), thiophene derivative (1 equiv), KOAc (1.5 equiv), KOH (1.5 equiv). [d] 120 °C. [e] Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), thiophene derivative (2 equiv), KOAc (1.5 equiv), DMAc, 20 h, 150 °C.

a mixture of KOH and KOAc as the bases (Table 3, entries 1 and 2). Using these conditions, only the 2-arylated products **16a** and **17a** were isolated. No formation of the other regioisomers or diarylated thiophenes was detected. As expected, the direct arylation of 3-amino-4-methylthiophene also gave regioselectively **16a**, **17a**, or **1d** in good yields (Table 3, entries 3−5). This high regioselectivity in favor of the arylation on carbon C2 might be due either to the coordination of the amino substituent to palladium or the electronic factors.

It should be noted that products **1c** or **17b** can be obtained in good yields by decarboxylation of **1a** or **13** using basic

Scheme 3



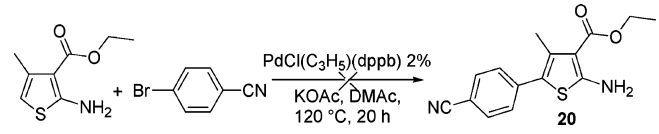
conditions (Scheme 3). Therefore, the presence of the ester substituents on carbon C2 of thiophene appears to be useful to block this reactive carbon and to provide alternative regioisomeric arylthiophenes.

We also performed a 2,5-diarylation reaction using 2 equiv of the aryl bromide, 1 equiv of the thiophene derivative, and a mixture of KOH and KOAc as the base (Table 3, entry 6). The target product **1b** was obtained in 70% yield. The synthesis of nonsymmetrically 2,5-diarylated thiophenes is also possible. Compound **17b** reacted with 4-bromotoluene gave **18** in 75% yield (Table 3, entry 7).

As the amino substituent on thiophenes appears to have a very strong directing effect in the course of direct arylation reactions, the regioselectivity of the coupling with methyl 3-aminothiophene-2-carboxylate was unpredictable. In the presence of 1-bromonaphthalene, we observed the formation of a mixture of the 4- and 5-arylated products **19a** and **19b** in 52% and 12% yields, respectively (GC ratio **19a**:**19b** = 77:23) (Table 3, entry 8).

Finally, we examined the influence of the substituent distribution on the thiophene ring. A permutation of the amino and ester substituents was found to drastically modify the thiophene reactivity. No formation of product **20** was detected in the presence of 4-bromobenzonitrile using similar reaction conditions (Scheme 4). This result reveals that the

Scheme 4



electronic effect of the amino group on thiophene is important.

In summary, we have demonstrated that when appropriate reaction conditions are employed the palladium-catalyzed direct arylation of some free NH_2-substituted thiophene derivatives proceeds nicely with a wide variety of aryl bromides.

To our knowledge, this is the first method for direct arylation of free NH_2-substituted thiophenes. The most reactive carbon for the direct arylations of 3-aminothiophenes appears to be the carbon C2. However, the presence of an ester substituent on C2 was found to be useful to block this highly reactive position to provide the 5-arylated thiophenes.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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