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Direct thiophene arylation catalysed by Palladium

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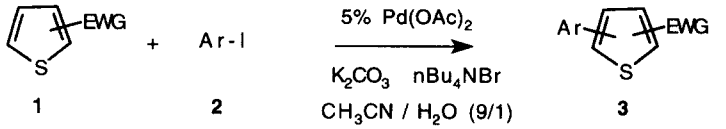
Abstract: Direct thiophene arylation using a Heck-type reaction with $Pd(OAc)_2/NBu_4Br$ as catalytic system is reported. Reactions with 2- and 3-substituted thiophenes have shown that substituent nature and position influence the cross-coupling. In particular, the substitution is regiospecific when the heterocycle is 2-substituted with an electron withdrawing group. © 1997 Published by Elsevier Science Ltd.

Since the discovery of electrical conductivity in oxidatively doped polyacetylene[1], the conjugated polymers have given rise to great interest. New structures based on aromatic precursors, especially thiophenes[2], and pyrroles[3] have been developed. The functionalization of electronic conducting polymers has powerful applications for modification of electrode surfaces and for electronic and opto-electronic applications[4]. The electronic properties of the material are dependent on the structure's flatness[5]. So, regioselective methods are needed to obtain a structurally homogeneous head-to-tail (HT) arrangement in which steric interactions are limited[6]. Regioselective synthesis of thiophene oligomers can be carried out using methods described by Suzuki[7], Kumada[8] or Stille[9]. However, these technics proceed in two steps via an organometallic intermediate and their chemocompatibility is often limited. As the chemistry of thiophene oligomers offers large applications in the field of electronic conducting polymers, the search for a new and easier way to prepare them is still a topical issue. The palladium-catalysed cross-coupling reactions of aryl bromides with thiophene were previously studied by Ohta and coll.[10]. Reactions were performed in N,N-dimethylacetamide at 150°C in a sealed tube and they tested non substituted thiophene as substrate.

In this work, we report that thiophenes **1** can be arylated by the Heck method using Jeffery conditions[11]. Indeed, the substitution reaction of activated thiophenes in position 2 or 3 by iodoaryle compounds was successfull. Reactions were performed in a mixture of acetonitrile and water (9/1) in the presence of a combination of tetra-n-butyl ammonium bromide, potassium carbonate and catalytic amounts of palladium acetate (scheme 1).



1 2 3

Scheme 1 : Arylation of Thiophene **1**

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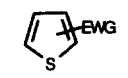
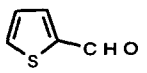
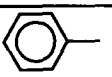
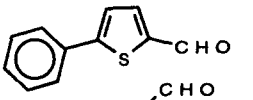
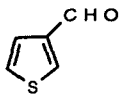
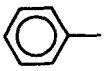
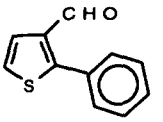
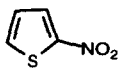
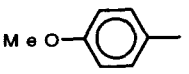
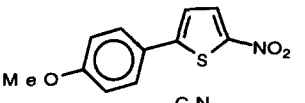
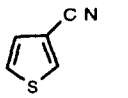
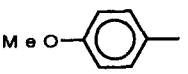
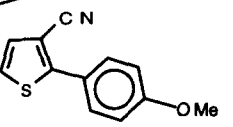
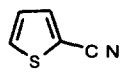
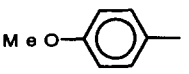
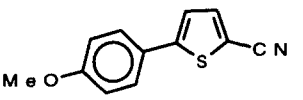
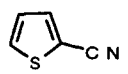
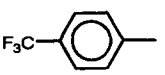
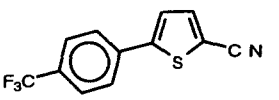
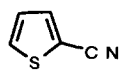
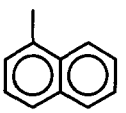
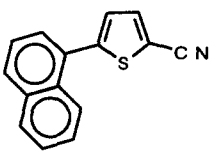
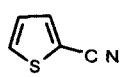
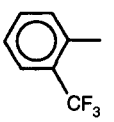
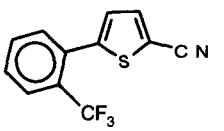
Table 1 : Arylation of Activated Thiophenes

Entry		Ar-I **2**	Time (hours)	Product **3a-h**	yields (%) GC(isolated)
a			7		41(30)
b			3.5		77(35)
c			54		61(37)
d			2.5		65(30)
e			4		89(77)
f			3.25		85(79)
g			4		94(77)
h			3		96(81)

Investigation of arylation of substituted thiophenes has shown that the nature and the position of the substituent influence the cross-coupling (table 1). Arylations of thiophenes bearing an aldehyde or a nitro function at position 2 or 3 were first investigated (entries a, b and c). The reaction of 3-substituted thiophenes is regioselective at position 2 which is activated by both sulfur and conjugation with aldehyde. However, formation of a minor isomer, resulting from the substitution at position 4, and a 2,4-disubstituted product were also observed. On the contrary, thiophenes substituted at position 2 are subjected to a regiospecific arylation at position 5. In this case, only one regio-isomer is obtained. In spite of this regiospecificity, 2-substituted thiophenes are less reactive (entries a and c) than their 3-substituted counter parts (entry b). Furthermore, yields of reactions are limited by the instability of the aldehyde or nitro function. The use of cyano as activating group

increases rates and yields of reactions. Also, in the case of 3-cyano thiophene (entry d), yields are limited by the non regiospecific substitution which leads to the formation of disubstituted product. As could be expected, the arylation of 2-cyano thiophene proceeds regiospecifically at position 5 and leads to good isolated yields (entries e, f, g and h). It is noteworthy that the substitution rate and kinetic are not really sensitive to electronic effects on the aryle adduct because yields and reaction times are similar with electron donating or withdrawing substituents on the iodoaryle moiety (entries e, f and g). We can also note that the aryle coupling is not affected by steric hindrance (entries g and h).

Concluding, we have developed a one step thiophene arylation with $Pd(OAc)_2$ / nBu_4NBr as catalytic system. The reaction proceeds with moderate yields with 2-carboxaldehyde thiophene and best results were obtained with 2-cyanothiophene because of a fast and regiospecific substitution. Among the synthesized products, **3c** and **3e** are conjugated systems bearing a donor group, a methoxy moiety, at one end and an acceptor group, respectively a nitro or cyano moiety, at the other end. This typical structure is characteristic of highly polarisable push-pull conjugated systems[12] and these compounds should lead to materials displaying optical non-linearity[13]. Compared to usual reactions, the large chemocompatibility of our method allows the synthesis of thiophene oligomers bearing various functional groups such as carboxaldehyde, cyano or nitro.

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14. Typical procedure : A suspension of potassium carbonate (40 mmoles) tetra-n-butyl ammonium bromide (16 mmoles) and palladium acetate (0,8 mmoles) in an acetonitrile and water mixture(3,7 ml / 0,4 ml) was

stirred under nitrogen for 5 minutes. Substituted thiophene **1** (32 mmoles) and iodoaryle **2** (16 mmoles) were successively added. The mixture was heated at 80°C for the time indicated. After cooling to room temperature, water and ether were added. The organic phase was washed with water and dried over $MgSO_4$. After removal of the solvent under vacuum, the substitution product was purified by column chromatography or recristalization.

3a Isolated yield : 30%; yellow solid; mp= 89°C; ^1H NMR (200MHz, $CDCl_3$) δ 7.39 (1H, d, J = 4 Hz), 7.40 (2H, dd, J = 7.1 Hz and J = 8.1 Hz), 7.42 (1H, dd, J = 1 Hz and J = 8.1 Hz), 7.66 (2H, dd, J = 7.1 Hz and J = 1 Hz), 7.72 (1H, d, J = 4 Hz), 9.88 (1H, 1s); ^{13}C NMR (50MHz, $CDCl_3$) δ 124.1 (CH), 126.4 (CHarom), 129.2 (CHarom), 129.4 (Carom), 133.0 (Carom), 137.4 (CH), 142.5 (C), 154.3 (C), 182.8 (CHO); HRMS calcd for $C_{11}H_8OS$ (M^+) : 188.0295868, found : 188.0296000.

3b Isolated yield : 35%; colorless oil; ^1H NMR (200MHz, $CDCl_3$) δ 7.26 (1H, d, J = 5.4 Hz), 7.48 (5H, m), 7.56 (1H, d, J = 5.4 Hz), 9.87 (1H, s); ^{13}C NMR (50MHz, $CDCl_3$) δ 125.1 (CH), 126.6 (CH), 128.9 (CHarom), 129.4 (Carom), 130.1 (CHarom), 131.4 (Carom), 137.1 (C), 156.1 (C), 185.8 (CHO); HRMS calcd for $C_{11}H_8OS$ (M^+) : 188.0295868, found : 188.0293000.

3c Isolated yield : 37%; orange solid; mp= 135°C; ^1H NMR (200MHz, $CDCl_3$) δ 3.86 (3H, s), 6.96 (2H, d, J = 8.9 Hz), 7.13 (1H, d, J = 4.3 Hz), 7.57 (2H, d, J = 8.9 Hz), 7.88 (1H, d, J = 4.3 Hz); ^{13}C NMR (50MHz, $CDCl_3$) δ 55.5 (CH_3), 114.2 (C), 114.9 (CHarom), 121.2 (CH), 124.8 (Carom), 127.8 (CHarom), 130.0 (CH), 152.5 (C), 161.3 (Carom); HRMS calcd for $C_{11}H_9NO_3S$ (M^+) : 235.0303151, found : 235.0319000.

3d Isolated yield : 30%; white solid; mp= 45.5°C ; ^{13}C NMR (50MHz, $CDCl_3$) δ 55.5 (CH_3), 105.1 (C), 114.7 (CHarom), 116.2 (CN), 123.9 (Carom), 124.5 (CH), 129.2 (CHarom), 130.2 (CH), 154.1 (C), 160.9 (Carom) ; HRMS calcd for $C_{12}H_9NOS$ (M^+) : 215.0404858, found : 215.0412000.

3e Isolated yield : 77%; brown solid; mp = 105.5°C; ^1H NMR (200MHz, $CDCl_3$) δ 3.83 (3H, s), 6.93 (2H, d, J = 8.1 Hz), 7.14 (1H, d, J = 3.9 Hz), 7.50 (2H, d, J = 8.1 Hz), 7.62 (1H, d, J = 3.9 Hz); ^{13}C NMR (50MHz, $CDCl_3$) δ 55.5 (CH_3), 106.9 (C), 109.9 (CN), 114.7 (CHarom), 122.2 (CH), 125.0 (Carom), 127.8 (CHarom), 138.5 (CH), 151.9 (C), 160.7 (Carom); HRMS calcd for $C_{12}H_9NOS$ (M^+): 215.0404858, found: 215.0409000.

3f Isolated yield : 79% ; yellow solid ; mp = 108°C ; ^1H NMR (200MHz, $CDCl_3$) δ 7.36 (1H, d, J = 4.0 Hz), 7.63 (1H, d, J = 4.0 Hz), 7.71 (4H, s) ; HRMS calcd for $C_{12}H_6F_3NS$ (M^+) : 253.0173058, found : 253.0151000.

3g Isolated yield : 77% ; yellow solid ; mp = 76°C ; ^1H NMR (200MHz, $CDCl_3$) δ 7.24 (1H, d, J = 3.8 Hz), 7.54 (4H, m), 7.70 (1H, d, J = 3.8 Hz), 7.93 (2H, m), 8.07 (1H, m); ^{13}C NMR (50MHz, $CDCl_3$) δ 109.4 (CN), 114.2 (C), 124.8 (Carom), 125.2 (Carom), 125.6 (CH), 126.5 (Carom), 127.2 (Carom), 127.6 (Carom), 128.6 (Carom), 129.7 (Carom), 129.9 (Carom), 131.3 (Carom), 133.8 (Carom), 137.6 (CH), 149.6 (C); HRMS calcd for $C_{15}H_9NS$ (M^+) : 235.0455712, found : 235.046600.

3h Isolated yield : 81% ; yellow solid ; mp = 48°C ; ^1H NMR (200MHz, $CDCl_3$) δ 7.12 (1H, d, J = 3.9 Hz), 7.48 (1H, m), 7.60 (3H, m), 7.80 (1H, m); ^{13}C NMR (50MHz, $CDCl_3$) δ 110.4 (C), 113.9 (CN), 123.6 (CF_3, q, $^1J_{CF}$ = 272 Hz), 126.8 (CHarom, q, $^3J_{CF}$ = 5.4 Hz), 128.3 (CHarom, q, $^4J_{CF}$ = 2.5 Hz), 129.4 (Carom, q, $^2J_{CF}$ = 30 Hz), 129.6 (CH), 130.9 (Carom, q, $^3J_{CF}$ = 1.9 Hz), 131.8 (CHarom), 133.0 (CHarom), 137.2(CH), 147.1(C); HRMS calcd for $C_{12}H_6F_3NS$ (M^+) : 253.0173057, found : 253.0182000.

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