Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 47 (2006) 9249–9252
Tetrahedron Letters

Direct C–H arylation of 3-methoxythiophene catalyzed by Pd. Application to a more efficient synthesis of π-alkoxy-oligothiophene derivatives

A. Borghese,* G. Geldhof and L. Antoine

Chemical Product Research and Development, Lilly Development Centre S.A., 1348 Mont-Saint-Guibert, Belgium

Received 29 September 2006; revised 24 October 2006; accepted 25 October 2006

Abstract—The direct regioselective C–H arylation of 3-methoxythiophene and 3,4-ethylenedioxythiophene (**EDOT**) was performed successfully under 'Heck-type' experimental conditions. This novel synthetic methodology has been used to prepare in a more simple way a series of oligothiophenes interesting for the electronic industry to build new synthetic organic materials.

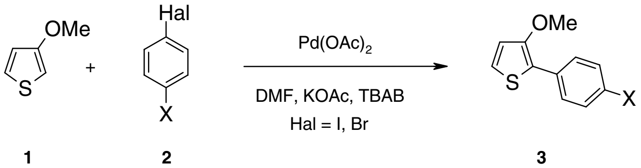
During the chemical development of a selected pharmaceutical candidate, an efficient synthesis of 2-aryl-thiophene derivative was required. We discovered that 3-methoxythiophene was easily arylated with iodo or bromo aryl derivatives under 'Heck-type' experimental conditions (Jeffery conditions).[1] This new and simple method affording biaryl compounds, contrast with the usual arylation methods involving a metal-catalyzed cross-coupling reaction of organometallics and organic halides (Stille, Kumada, and Suzuki-type).[2] Recently, a work aimed at finding a general catalysis (rhodium complex catalyst bearing a strongly π-accepting ligand, $P[OCH(CF_3)_2]_3$) to perform the direct C–H arylation of (hetero)arenes, including 3-methoxythiophene was reported.[3] The direct arylation of thiophene bearing electron-withdrawing groups was previously published by Lemaire and co-workers.[4] Similarly, a Chemical Development group at GSK described[5] the regioselective arylation of 3-thiophenecarboxylate methyl ester by an aryl bromide derivative, catalyzed by $Pd(PPh_3)_4$. We report here the ligand-free arylation of 3-methoxythiophene catalyzed by $Pd(OAc)_2$ or $PdCl_2$ to give in a high regioselective manner the 2-aryl, 3-methoxy thiophene derivatives **3**. Moreover, as that reaction will find its application in the field of alkoxy-thiophene-based oligomers preparation, we also report herein the facile preparation of some selected π-alkoxy-oligomers.

The reaction is performed in *N*,*N*-dimethylformamide (DMF) in the presence of KOAc, $t\text{-}Bu_4NBr$ (TBAB), and catalytic amounts of $Pd(OAc)_2$ at 80 °C with either aryl iodide or bromide derivatives (Scheme 1).

Several 2-aryl 3-methoxythiophenes **3a**–**g** have been prepared by the arylation of **1** using a series of substituted bromo-aryl derivatives **2a**–**g** (Table 1).

The high selectivity observed in the polar solvent (DMF) for the arylation reaction might be explained by the following reaction mechanism (Scheme 2).[7] According to a similar reasoning[5] that was put forward for the arylation of 3-carboalkoxy furan and thiophene, DMF would favor the ionization of the Ar–Pd–X into the $Ar–Pd^+ X^-$ species **a**.

The electrophilic species **a** would react at the electron-rich 2-position of the 3-methoxythiophene, giving the cationic intermediate **b**, which after proton abstraction and reductive elimination would afford the 2-arylated product **3**.



Scheme 1. Arylation of 3-methoxythiophene **1**.

---

* Corresponding author. Tel.: +32 10 476 309; fax: +32 10 476 315; e-mail: a.borghese@lilly.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.130

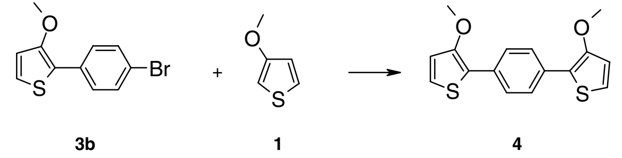
Table 1. Arylation of thiophene **1**[6]

Entry	Br–Ar–X (**2a**–**g**)	Product (**3**)	Yield[a] (%)
1	(**2a**) 4-Cl	(**3a**)	60[b]
2	(**2b**) 4-Br	(**3b**)	28[c]
3	(**2c**) 4-CO_2Et	(**3c**)	56
4	(**2d**) 4-CN	(**3d**)	53
5	(**2e**) 4-OMe	(**3e**)	41
6	(**2f**) 4-NO_2	(**3f**)	73
7	(**2g**) 3-NO_2	(**3g**)	48

[a] Isolated yield are not optimized. Each compound has been purified by flash chromatography and characterized.

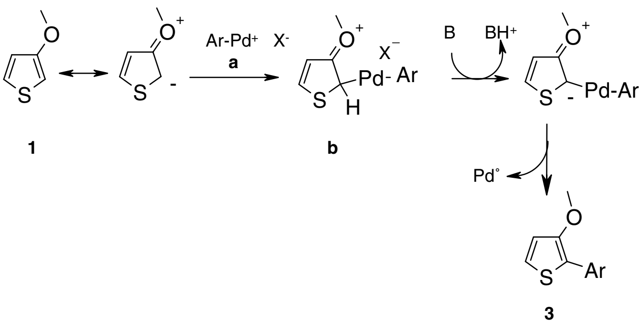
[b] We did not observe the formation of triaryl derivative **4** with 4-bromochlorobenzene (entry 1).

[c] The low isolated yield is mainly due to the formation of triaryl compound **4**.



During our investigation, we found that $Pd(PPh_3)_4$ was not an active catalyst, contrary to what is reported for the direct arylation of 3-thiophene carboxylate methyl ester.[5] This lack of reactivity would be explained by a too high stabilization of the Pd^{II} electrophilic species **a** by the PPh_3 ligand. However, $Pd(dba)_2$ catalyzed the arylation reaction, thus confirming that Pd^0 is the catalytic species. We also found that aryls bearing electron-withdrawing groups react faster than aryls substituted by electron-donating groups as already reported.[5] In a competitive arylation experiment of **1** by **2e** and **2f**, only **3f** was formed. The aryl EW-groups would favor the oxidative insertion of the Pd^0 into the aryl C–halogen bond.

Today, there is a considerable interest related to the preparation of π-conjugated oligomers such as oligothiophenes for their potential application as building blocks to construct new polymers having original properties useful for the electronic industry. More particularly, polymers based on 3-alkoxythiophene are interesting due to their promising electronic and optical properties.[8] Typically, the oligothiophenes and polymers are prepared by cross-coupling reactions. We took advantage of the easy arylation of 3-methoxythiophene **1** to extend this synthetic methodology to the preparation of unsymmetrical bithienyls **6** (Scheme 3). The palladium-catalyzed reaction of 2-bromo-thiophene (**5a**, 1 equiv) or 2-bromo-3-methylthiophene (**5b**, 1 equiv) with **1** in DMF gives, respectively, the 3-methoxy bithienyl derivatives **6a** and **6b** in 61% and 35% yields.



Scheme 2. Tentative explanation of the origin of the 2-arylation selectivity.

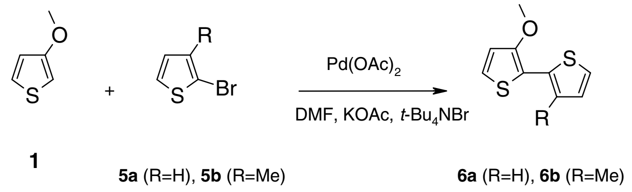
This new synthetic methodology was also applied for the preparation of the known[9] 3-methoxythiophene-based oligomers; quaterthienyl **7**, terthienyl **8** and the new mixed thienyl-phenylene **9** (Scheme 4). Compounds **7** and **8** were previously prepared by cross-coupling reactions. Palladium-catalyzed reaction of **1** with dihalogenated aryls, 2,5-bromo thiophene, 5,5′-dibromo-2,2′-bithienyl and 4,4′-dibromobiphenyl afford **9**, **8** and **7** in 23%, 29%, and 28% yields, respectively, after flash chromatography.[10]

In the field of new organic conducting material, 3,4-ethylenedioxythiophene (**EDOT**) is a building block frequently used.[11–13] The preparation of (**EDOT**) oligomers can also benefit from this new developed technology, thus avoiding cross-coupling reactions. **EDOT** is a 3,4-disubstituted alkoxy thiophene where positions 2 and 5 will display similar reactivities during the arylation reaction to afford di-substituted **EDOT** derivatives.

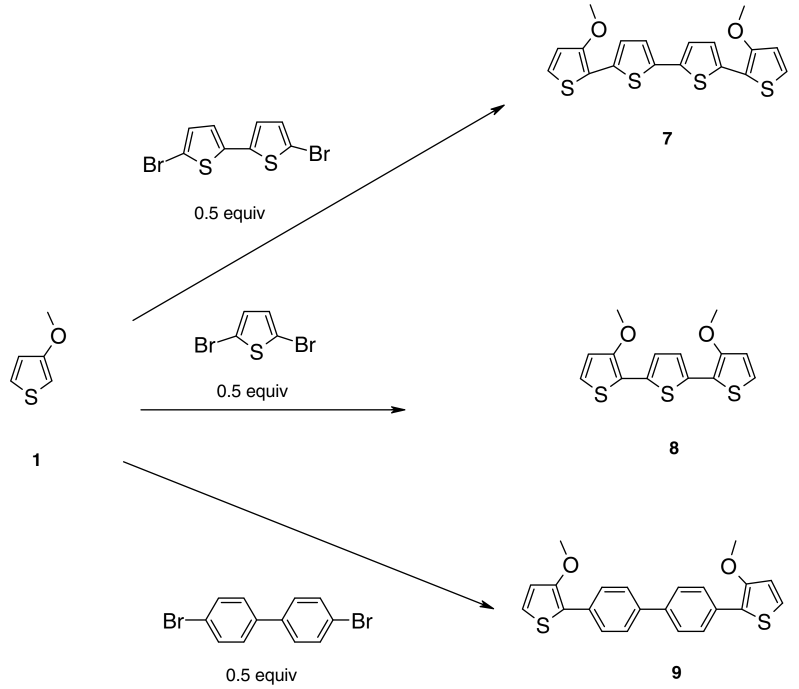
We have exemplified this new synthetic methodology by the preparation of terthienyl **11** and the mixed aromatic-thienyl **12** (Scheme 5). The reaction of **EDOT** with either 2-bromothiophene or ethyl 4-bromobenzoate afford, respectively, **11**[14] and **12**[15] in 40% and 92% yields.

Another more elaborate example is given by the preparation of the mixed conjugated quaterthienyls **15**[16] of thiophene and **EDOT** (Scheme 6). It is synthesized by the palladium-catalyzed direct arylation of 5-bromo-3,4-ethylenedioxy-2,2′-bithienyl **14** by 3,4-ethylenedioxy-2,2′-bithienyl **13**. These two key intermediates are in turn prepared by a palladium-catalyzed direct arylation of a molar excess of **EDOT** with 2-bromothiophene in DMF to give 3,4-ethylenedioxy-2,2′-bithienyl **13** in a 40% yield. Bromination of **13** with NBS in dimethylacetamide (DMA) performed according to a described procedure[12] gives **14**. Compound **15** has been prepared in 27.5% from **EDOT**.

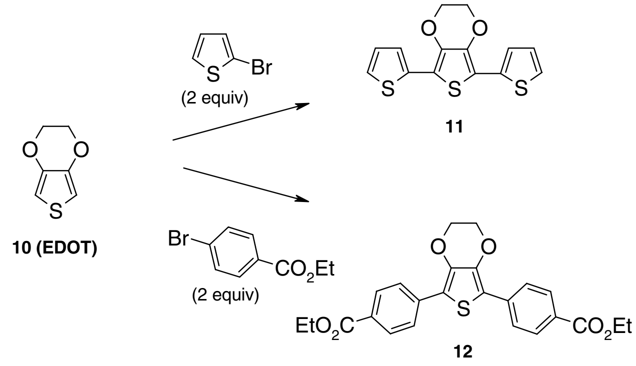
The scope of that reaction could be extended to the polymerization reaction to prepare novel polymeric materials or for example to improve the preparation of known polymers such as poly(3,4-ethylenedioxythiophene) (**PEDOT**). **PEDOT** is a commercially available conducting polymeric material having numerous technological applications that could be prepared according



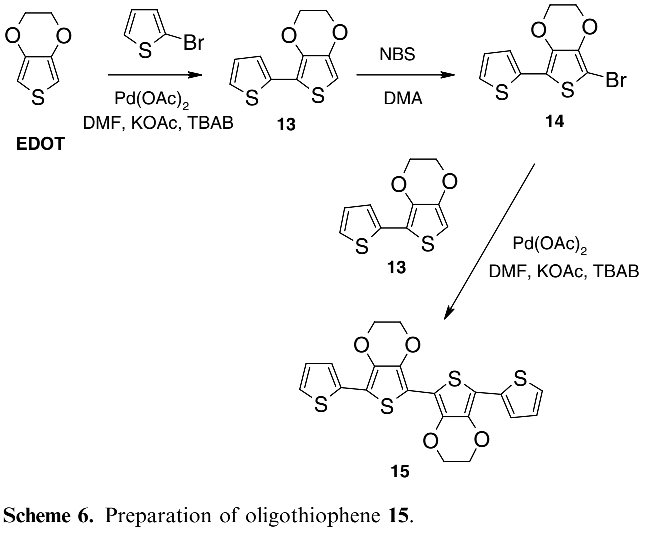
Scheme 3. Preparation of unsymmetrical bithienyls.



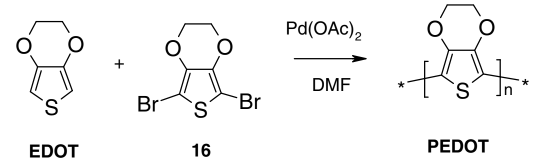
Scheme 4. Synthesis of selected thiophene-based oligomers.



Scheme 5. Synthesis of **EDOT**-based oligothiophenes.



Scheme 6. Preparation of oligothiophene **15**.



Scheme 7. Proposed new preparation of **PEDOT**.

to our new synthetic methodology by reacting the 2,5-dibromo-3,4-ethylenedioxythiophene **16** with **EDOT** (Scheme 7). Mixed aryl-EDOT polymeric material could also be prepared by using biarylated derivative, allowing the preparation of a new polymeric materials.

To summarize, we have developed a highly efficient direct C–H arylation reaction of 3-alkoxythiophene derivatives, thus avoiding the classical cross-coupling reactions, using commercially available catalysts $Pd(OAc)_2$ or $Pd(Cl)_2$. We have applied that new synthetic methodology to the preparation of alkoxy-thiophene based oligomers and demonstrated its usefulness and simplicity. This new procedure could facilitate the development of new polymeric material having the requisite electronic and optical properties.

Acknowledgments

We thank Dr. P. Delbeke and Mr. Cl. Delatour for having performed the ^{1}H NMR and HRMS analysis.

References and notes

1. Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

2. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
3. Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748–11749.
4. Gozzi, C.; Lavenot, L.; Ilg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Lett.* **1997**, *38*, 8867–8870.
5. Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Timoschenko, M. F. *Org. Lett.* **2003**, *5*, 301–304.
6. *Typical operating procedure to prepare* **3a**–**g**:
   To a stirred solution of 3-methoxythiophene (1 g, 8.76 mmol, 1 equiv) in DMF (20 mL) was added potassium acetate (2.58 g, 3 equiv), *tert*-butylammonium bromide (2.82 g, 1 equiv) and the desired arylbromide (1 equiv) and finally $\mathrm{Pd(OAc)_2}$ (200 mg, 0.1 equiv). The resulting suspension was heated at a temperature of 80 °C till completion of the reaction as checked by HPLC. After completion of the reaction, the mixture was cooled down to 20 °C and $\mathrm{CH_2Cl_2}$ (25 mL) and water (25 mL) were added. The organic layer was separated and concentrated. The resulting dark oil was purified by flash chromatography on silica gel eluted with *n*-heptane/ethyl acetate gradient to yield the desired product as an oil or a solid. The lower amounts of catalyst (2 wt %) work equally well, especially with EW-substituted bromoaryl derivatives.
7. Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72.
8. Shi, C.; Yao, Y.; Yang, Y.; Pei, Q. *J. Am. Chem. Soc.* **2006**, *128*, 8980–8986.
9. Miller, L. L.; Yu, Y. *J. Org. Chem.* **1995**, *60*, 6813–6819.
10. The reported isolated yields represent only the pure fraction isolated by flash chromatography.
11. Turbiez, M.; Frère, P.; Blanchard, Ph.; Roncali, J. *Tetrahedron Lett.* **2000**, *41*, 5521–5525.
12. Apperloo, J. J.; Groenendaal, L.; Verheyen, H.; Jayakannam, M.; Janssen, R. A. J.; Dkhissi, A.; Beljonne, D.; Lazzaroni, R.; Brédas, J.-L. *Chem. Eur. J.* **2002**, *8*, 2384–2396.
13. Pai, Ch.-L.; Liu, Ch.-L.; Chen, W.-Ch.; Jenekhe, S. A. *Polymer* **2006**, *47*, 699–708.
14. Mathieu, T.; Pierre, F.; Magali, A.; Christine, V.; Joerg, A.; Roncali, J. *Chem. Eur. J.* **2005**, *11*, 3742–3752.
15. *Preparation of terthienyl* **12**:
    To a stirred solution of ethyl 4-bromobenzoate (4.29 g, 18.71 mmol, 2 equiv) in DMF (20 mL) was added 3,4-ethylenedioxithiophene (1.33 g, 9.35 mmol, 1 equiv), potassium acetate (2.75 g, 3 equiv), *tert*-butylammonium bromide (TBAB) (3.02 g, 1 equiv), and $\mathrm{Pd(OAc)_2}$ (210 mg, 0.1 equiv). The mixture was then heated at 80 °C for 1 h. The reaction was cooled down till 20 °C and $\mathrm{CH_2Cl_2}$ (25 mL) and water (25 mL) was added. After decantation and separation, the organic layer was evaporated to dryness and the residue was taken in ethanol (20 mL). The resulting suspension was stirred at 20 °C and filtered to give 3.81 g of **12** as a brown solid.
16. Mohanakrishnan, A. K.; Hucke, A.; Lyon, M. A.; Lakshmikantham, M. V.; Cava, M. P. *Tetrahedron* **1999**, *55*, 11745–11754.