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Facile Synthesis of 3-Alkoxy-4-cyanothiophenes As New Building Blocks for Donor–Acceptor Conjugated Systems

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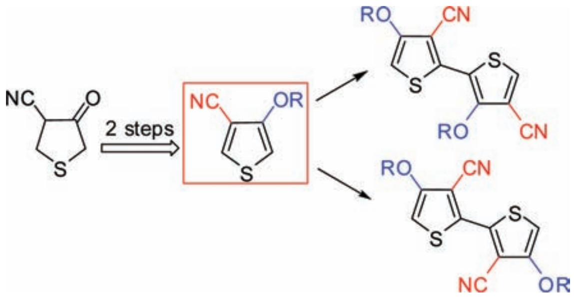
ABSTRACT



3-Alkoxy-4-cyanothiophenes are efficiently synthesized in two steps from the readily available 4-cyano-3-oxotetrahydrothiophene. Regioisomers of bithiophene derivatives are easily synthesized by playing on the strong electronic dissymmetry of the thiophene ring induced by the alkoxy and cyano groups.

Low band gap conjugated systems have been a focus of sustained interest for many years.[1,2] Initially motivated by fundamental problems related to the posssibility of synthesizing a true organic metal by progressive closure of the energy gap,[1] the topic has received renewed interest in the context of organic solar cells.[2] The synthesis of new materials with low band gap (Eg) values and also broad absorption bands represents one of the most efficient strategies to develop organic solar cells with higher efficiencies.[2] The synthetic principles for band gap control of conjugated systems resort roughly to three main approaches:[1] (i) rigidification of the conjugated system,[3,4] (ii) increase of the quinoid character of the aromatic basic units,[5] and (iii) introduction of alternant electron-donating (D) and electron acceptor (A) groups on the conjugated backbone.[6] A major advantage of the D/A approach lies in the possibility of finely tuning the band gap of the polymer by modifying the spatial extension, ratio, and sequential

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(1) (a) Roncali, J. *Chem. Rev.* **1997**, *97*, 730.

(2) (a) Chen, Y.-J.; Yang, S.-H.; Hsu, C.-S. *Chem. Rev.* **2009**, *109*, 5868. (b) Chen, J.; Cao, Y. *Acc. Chem. Res.* **2009**, *42*, 1709. (c) Roncali, J. *Macromol. Rapid Commun.* **2007**, *28*, 1761. (d) Po, R.; Maggini, M.; Camaioni, N. *J. Phys. Chem. C* **2010**, *114*, 695.

(3) For examples of rigidification by a covalent bridge, see: (a) Roncali, J.; Thobie-Gautier, C. *Adv. Mater.* **1994**, *6*, 846. (b) Blanchard, P.; Brisset, H.; Riou, A.; Roncali, J. *J. Org. Chem.* **1997**, *62*, 2401. (c) Blanchard, P.; Verlhac, P.; Michaux, L.; Frère, P.; Roncali, J. *Chem.—Eur. J.* **2006**, *12*, 1244.

(4) For examples of rigidification by nonbonded intramolecular interactions, see: (a) Turbiez, M.; Frère, P.; Roncali, J. *J. Org. Chem.* **2003**, *68*, 5367. (b) Turbiez, M.; Frère, P.; Allain, M.; Videlot, C.; Ackermann, J.; Roncali, J. *Chem.—Eur. J.* **2005**, *11*, 3742. (c) Spencer, H. J.; Skabara, P. J.; Giles, M.; McCullough, I.; Coles, S. J.; Hursthouse, M. B. *J. Mater. Chem.* **2005**, *15*, 4783. (d) Turbiez, M.; Hergué, N.; Leriche, P.; Frère, P. *Tetrahedron Lett.* **2009**, *50*, 7148.

(5) (a) Wudl, F.; Kobayashi, M.; Heeger, J. A. *J. Org. Chem.* **1984**, *49*, 3382. (b) Brédas, J. L. *J. Chem. Phys.* **1985**, *82*, 3808. (b) Karsten, B. P.; Janssen, R. A. J. *Org. Lett.* **2008**, *10*, 3513.

(6) (a) Havinga, E. E.; ten Hoeve, W.; Wynberg, H. *Polym. Bull.* **1992**, *29*, 119. (b) Karikomi, M.; Kitamura, C.; Tanaka, S.; Yamashita, Y. *J. Am. Chem. Soc.* **1995**, *117*, 6791. (c) Zoombelt, A. P.; Fonrodona, M.; Turbiez, M. G. R.; Wienk, M. M.; Janssen, R. A. J. *J. Mater. Chem.* **2009**, *19*, 5336.

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arrangement of the donor and acceptor blocks in the conjugated chain. However, combining donor and acceptor blocks with multiple possible variations poses the question what are the structural limits of this approach. Whereas an extended push−pull molecule with D and A groups connected by a conjugating linker represents one limiting case, the other limit would involve a system in which D and A groups alternate on every carbon of the conjugated chain. Taking polythiophene as a model, the realization of this maximum possible D−A alternation imposes that the D and A groups must be introduced on the same thiophene unit. In this context, 3-alkoxy-4-cyanothiophenes **1** represent interesting building blocks since both substituents combine strong donor or acceptor strength with low steric demand (Figure 1).[7]

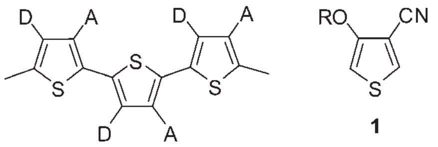
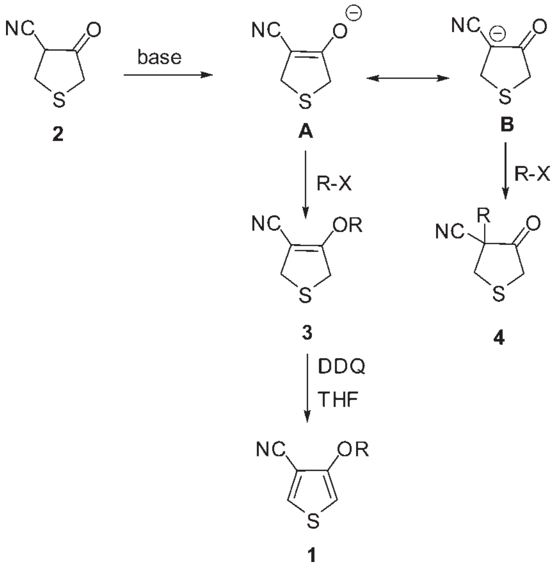


Figure 1. Limit structures in D−A approach.

We have recently described the synthesis of 3-methoxy-4-cyanothiophene in two steps from 3,4-dibromothiophene.[8] After substitution of the first bromo atom by the methoxy group, the introduction of the cyano group was performed with an excess of cyanide anion under microwave irradiation. However, extension of this method to longer alkoxy chains was limited by the difficulty in synthesizing the intermediate 3-alkoxy-4-bromothiophene derivatives.[9] As a further step, we report here a new rapid and efficient synthetic approach for the preparation of 3-alkoxy-4-cyanothiophene derivatives **1** based on O-alkylation of the readily accessible 4-cyano-3-oxotetrahydrothiophene **2**[10] followed by oxidative aromatization (Scheme 1).

The main difficulty resides in the selective O-alkylation reaction of the enolate anion **A** for obtaining dihydrothiophene derivatives **3** in good yields. Baraldi et al. mainly obtained C-alkylated derivatives **4** by treatment of **1** in dry acetone with alkyl halides in the presence of anhydrous potassium carbonate while the O-alkylated product was formed only in 5−10% yield.[11] Although O-alkylation of **2** by a methoxy group has been achieved by reaction with diazomethane[12] or with an ethoxycarbonylmethoxy group by a Mitsunobu reaction,[13] no simple and efficient general method has been reported so far.

Scheme 1. Synthetic Pathway for the Synthesis of **1**



The orientation to O-alkylation largely depends on the nature of the base and of the alkylating agent used for the nucleophilic substitution. The various conditions used for the synthesis of compounds **3** are gathered in Table 1.

As expected, the use of methyl iodide in the presence of K_2CO_3 as base gives **3a** in a very low yield (entry 1). The reactivity of the enolate anion can be improved to reach yields of ca. 35% by the addition of crown ether to the reaction medium (entry 2) or in the presence of a soft cation such as Cs^+ (entry 3).

The use of a stronger alkylating agent such as trifluoromethanesulfonate increases the yield of **3a** up to 55%. With a long-chain haloalkane in the presence of Cs_2CO_3 as a base, the reaction proceeds in a moderate yield of 40−45% for compound **3b** after 2 h at room temperature or 15 min at 80 °C but the yield decreases to 22% for the compounds containing branched alkyl chains (**3c**) (entries 4−7).

Application of microwave irradiation for enhancing nucleophilic substitutions has been demonstrated,[14] and herein we have examined if this method could increase the yield of O-alkylated compounds **3b** and **3c**.

Reactions were carried out by mixing compound **2** and an alkylating agent in DMF in the presence of Cs_2CO_3 as the base, and then the mixture was irradiated in an open vessel in a CME microwave oven. TLC showed the complete consumption of **2** after 2 min of irradiation. With hexyl iodide (entry 8), compound **3c** was isolated in 53% yield while a small amount (< 10%) of C-alkylated compound **4c** was also formed. A large increase of the O-alkylation yield was observed when a mesylate derivative was used as an alkylating agent. Thus,

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(7) (a) Demanze, F.; Yassar, A.; Garnier, F. *Adv. Mater.* **1995**, *7*, 907. (b) Ho, H. A.; Brisset, H.; Elandaloussi, E.; Frère, P.; Roncali, J. *Adv. Mater.* **1996**, *8*, 990. (c) Berson, S.; Cecioni, S.; Billon, M.; Kervella, Y.; de Bettignies, R.; Bailly, S.; Guillerez, S. *Solar Energy Mater. Solar Cells* **2010**, *94*, 699.

(8) Hergué, N.; Mallet, C.; Frère, P.; Allain, M.; Roncali, J. *Macromolecules* **2009**, *42*, 5593.

(9) Savitha, G.; Hergué, N.; Guilmet, E.; Allain, M.; Frère, P. *Tetrahedron Lett.* **2011**, *52*, 1288.

(10) Compound **2** is easily prepared by condensation of acrylonitrile on methylthioglycolate; see ref 11.

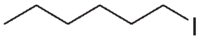
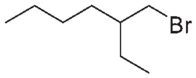
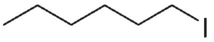
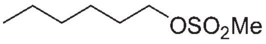
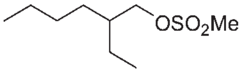
(11) Baraldi, P. G.; Pollini, G. P.; Zanirato, V. *Synthesis* **1985**, 969.

(12) Chou, T.-S.; Chang, C.-Y.; Wu, M.-C.; Hung, S.-H.; Liu, H.-M.; Yeh, W.-Y. *J. Chem. Soc., Chem. Commun.* **1992**, 1643.

(13) Redman, A. M.; Dumas, J.; Scott, W. J. *Org. Lett.* **2000**, *2*, 2061.

(14) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697.

Table 1. Optimization for the Synthese of O-Alkylated Compounds **3**

entry	alkylating agent	base	procedure	compd	yield[c]
1	MeI	K_2CO_3	A[a]	**3a**	< 10%
2	MeI	K_2CO_3	A + crown ether	**3a**	32%
3	MeI	Cs_2CO_3	A	**3a**	38%
4	CF_3SO_3Me	Cs_2CO_3	A	**3a**	55%
5		Cs_2CO_3	A	**3b**	49%
6			A		
7		Cs_2CO_3		**3c**	22%
8		Cs_2CO_3	B[b]	**3b**	55%
9		Cs_2CO_3	B	**3b**	95%
10		Cs_2CO_3	B	**3c**	71%

[a] Procedure A: 1 g of **2** + 1.2 equiv of base +1.2 equiv of RX in 10 mL of DMF strirred a rt for 2 h. [b] Procedure B: 1 g of **2** + 1.2 equiv of base +1.2 equiv of RX in 10 mL of DMF irradied for 2 mn (P = 70−100 W, T = 80 °C). [c] Isolated yield.

compounds **3c** and **3d** were isolated in 95% and 71% yields respectively (entry 9 and 10).

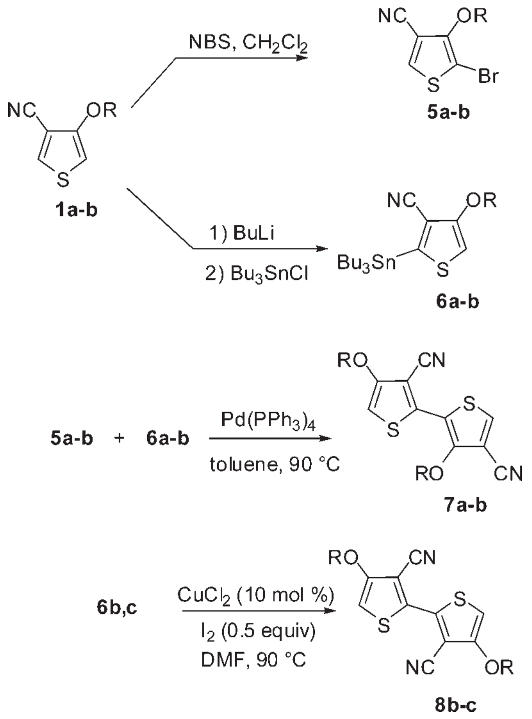
Aromatization of 3,4-disubstituted-2,5-dihydrothiophenes to the corresponding thiophene derivatives has been achieved with oxidants such as hydrogen peroxide,[15] sulfuryl chloride,[16] bromine,[17] and recently copper dibromide.[18] While oxidation of compounds **3** with sulfuryl chloride and hydrogen peroxide gives compounds **1** in less than 20% yield, the use of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gives the target compounds in 90−95% yield.

Thus, from the readily available compound **2**, the combination of microwave irradiation, a mesylate reagent, and oxidation with DDQ affords the target molecules in a 65−86% overall yield.

We next focused our attention on the different reactivities of the 2- and 5-positions of 3-alkoxy-4-cyanothiophenes **1**. The combined effects of the mesomeric electron donor effect of the methoxy group and the electron-withdrawing character of the cyano group create a large dissymmetry in the electron density of the thiophene ring at the 2- and 5-positions (Figure S1). Of course, such a situation is propitious to highly regioselective reactions (Scheme 2). Treatment of compounds **1** with 1 equiv of NBS leads to exclusive bromination at the 2-position which presents the highest electron density, leading to compound **5** in 80−85% yield. As revealed by ^1H NMR of compounds **1**, the strong difference between the chemical shifts of the two aromatic protons is an indication of their highly different acidity. The large deshielding of the proton adjacent to the cyano group (7.8 ppm) is associated with a stronger acidity, and reaction with a base such as *n*-BuLi[19] or LDA leads to selective deprotonation at the 5-position. Subsequent treatment of the lithiated derivative with tributylstannyl chloride gave stannic derivatives **6** in 90% yield.

Unsymmetrical bithiophenes **7a,b** have been prepared by Stille coupling of bromo and stannic compounds **5** and **6**. The reaction was carried out in toluene at 110 °C with $Pd(PPh_3)_4$ as a catalyst (10 mol %), and compounds **7a** and **7b** have been obtained in 55% yield. Small amounts of the symmetrical bithiophene **8** were also formed due to the homocoupling of the stannic compound.

Scheme 2. Synthesis of Bithiophenes **7** and **8**



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(15) Takaya, T.; Kosaka, S.; Otsuji, Y.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2086.

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(17) Dang, Y.; Chen, Y. *J. Org. Chem.* **2007**, *72*, 6901.

(18) Dang, Y.; Chen, Y. *Eur. J. Org. Chem.* **2007**, *2007*, 5661.

(19) It can be noted that the nucleophilic addition of *n*-BuLi on a cyano group has never been observed.

The symmetrical derivatives **8b,c** have been synthesized in 35% yield by favoring the homocoupling reaction of the stannic derivatives **6b,c** using a catalytic amount of $CuCl_2$ (10 mol %) and 0.5 equiv of I_2.[20]

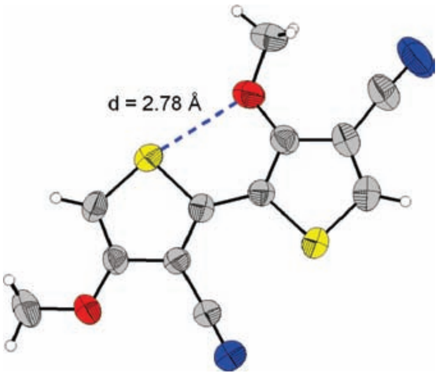

Figure 2. X-ray structure of compound **7a**. Ellipsoids are drawn at 50% probability level. The S---O intramolecular interaction is indicated by a dotted line.

The crystallographic structures of single crystals of **7a** and **8c** obtained by slow evaporation of chloroform−ethanol solutions have been analyzed by X-ray diffraction. Compound **7a** crystallizes in the monoclinic $P2_1/c$ space group. As shown in Figure 2 the two thiophene rings adopt a planar anti-conformation with a dihedral angle close to 1°. The S---O distance of 2.783(3) Å is considerably shorter than the sum of the van der Waals radii of sulfur and oxygen (1.85 Å + 1.40 Å = 3.25 Å) which is characteristic for noncovalent S---O intramolecular interactions leading to the self-planarization and rigidification of the π-conjugated system.[5] The molecules stack along the a-axis with cyano groups superimposed to methoxy ones (Figure S2). The distance between the planes of overlapping molecules is 3.51 Å.

Compound **8c** crystallizes in the triclinic $P\bar{1}$ space group. The structure is defined by two independent half molecules named **8c$_1$** and **8c$_2$**. The molecule **8c$_2$** presents a more important thermal agitation than **8c$_1$** for the atoms at the extremity of the branched alkyl chains. Both molecules adopt a planar anti-conformation (Figure 3). The molecules **8c$_1$** and **8c$_2$** stack in two different directions (Figure S3). The distances between the planes of two molecules of **8c$_1$** is d_1 = 3.63 Å while the distances between the cores of two molecules of **8c$_2$** is d_2 = 3.63 Å.

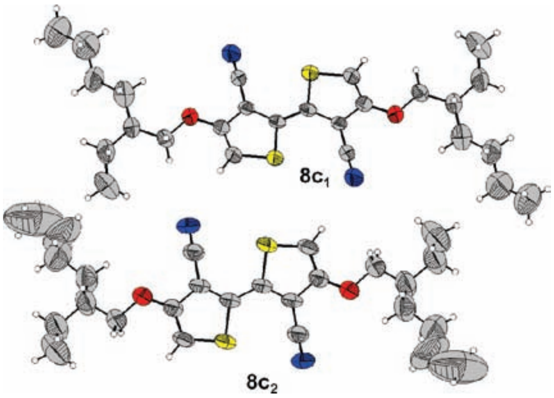

Figure 3. X-ray structure of compound **8c**. Ellipsoids are drawn at 50% probability level.

To summarize, we have developed a facile and efficient general method for the synthesis of 3-alkoxy-4-cyanothiophenes in two steps from the easily available 4-cyano-3-tetrahydrothiophene. The large dissymmetry introduced in the electron density of the thiophene ring allows straightforward regioselective substitution of the 2- or 5-position and thus makes it possible to use 3-alkoxy-4-cyanothiophenes as building blocks of new alternant donor−acceptor conjugated systems. The chain length dependence of the electronic properties of oligomers based on these new building blocks is under investigation and will be reported in future publications.

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Supporting Information Available. Experimental procedures and characterization data of compounds. Copies of ^1H and ^{13}C NMR of compounds **1**, **3**, **7**, and **8**. Theoretical calculation for compound **1a** and Figure S1. X-ray structures data and figures (pp S3 and S4) for compounds **7a** and **8c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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