Synthesis of bis-3,4-dialkoxythiophenes linked by a *m*-xylene bridge

Pablo A. Cisneros-Pérez [a,b], Bernardo A. Frontana-Uribe [a,c,*], Diego Martínez-Otero [a], Erick Cuevas-Yáñez [a]

[a] Centro Conjunto de Investigación en Química Sustentable, UAEMéx-UNAM, Carretera Toluca-Atlacomulco km 14.5, Campus UAEMéx, San Cayetano-Toluca, C.P. 50200 Estado de México, Mexico
[b] Universidad Regional Amazónica IKIAM, km 6 vía a Muyuna, Tena, Napo, Ecuador
[c] Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Ciudad de México 04510, Mexico

ABSTRACT

Two examples of bis 3,4-dialkoxythiophenes linked with a *m*-xylene bridge were synthesized in yields of 18% and 32% in a six step process. The formation of the *m*-xylene bridge, key reaction of the synthesis, was carried out through Williamson, Mitsunobu and *trans*-etherification reactions which were subsequently compared on performance and versatility. The Mitsunobu reaction assisted by sonication was found to be the best strategy. These molecules are among the few examples of unsymmetrically substituted 3,4-dialcoxythiophenes. During the synthesis an 18 member heterocycle, closely related to a crown ether was isolated. The details of the XRD structure of this heterocycle are discussed.

© 2016 Elsevier Ltd. All rights reserved.

Introduction

The 3,4-dialkoxythiophenes are a family of heteroaromatic molecules that have showed to be of great utility in the preparation of π–conjugated materials. They can be used as building blocks, oligomers, or polymers[1] in fabrication of organic electronic devices such OLEDs,[2a] OFETs,[2b] and OSCs.[2c] Most of these materials have been obtained using 3,4-dialkoxythiophenes in which, the alkoxide groups consist of equal aliphatic chains or, symmetrical and asymmetrical disubstituted chains. The alkoxide group is added to thiophene ring by one of three O-alkyalation methodologies: Williamson,[3a–c] Mitsunobu,[3d–g] or transetherification (from 3,4-dimethoxythiophene[4] and an alcohol,[5a] diol,[5b] or cathecol[5c]). Substitution with different alkoxide groups in positions 3 and 4 of the thiophene ring has not been studied deeply.[6] Asymmetrical 3,4-dialcoxythiophenes are rare compounds in the chemical literature, some of them were evaluated as drugs and were prepared by modifications in the aliphatic chain of 2,2-dimethyl-4-[3-(4-methoxythienyl)oxymethyl]-1,3-dioxolane.[7] Asymmetrical 3,4-dialcoxythiophenes may provide materials with unique properties. Asymmetrical model molecule was designed to develop a useful methodology to prepare unsym-metrical 3,4-dialkoxy derivatives. The model framework consisted of a bis-3,4-dialkoxythiophene linked by a *m*-xylene bridge system. The *m*-xylene moiety is frequently used to obtain arylether dendrimers,[8] and can act as a spacer among the two thiophene rings, a situation frequently observed in useful molecules in material science.[9] In this Letter the preparation of bis-3,4-dialkoxythiophenes linked by the *m*-xylene bridge, via the three different O-alkylation methodologies, is compared. As a result, new thiophene members of the rare family of unsymmetrically substituted 3,4-dialcoxythiophenes were prepared. Nevertheless, the compounds have symmetry due to the symmetrical ether bridge that is constructed.

Results and discussion

The bridged product **6** was very difficult to achieve directly through a Williamson reaction with **1**, α,α′-*m*-dibromoxylene, and Et₃N as base (Scheme 1).[3c] The purification of the mixture of reaction was extremely difficult, due the high polarity of **6** and by-products generated; only a 12% yield for **6** was achieved using this methodology. The monoalkylation of **1** with methyl and benzyl groups gave products **2a** (X = Me) and **2b** (X = Bn) in two steps of the reaction (see Supplementary content). Several experimental conditions were attempted with **2a** and α,α′-*m*-dibromoxylene to carry out the Williamson reaction, all of them without promising results (Table 1).[3c,10] Again, the reactions resulted in low yields and complicated purifications. Compound

* Corresponding author at: Centro Conjunto de Investigación en Química Sustentable, UAEMéx-UNAM, Carretera Toluca-Atlacomulco km 14.5, Campus UAEMéx, San Cayetano-Toluca, C.P. 50200 Estado de México, Mexico. Tel.: +52 722 276 6610.
E-mail address: bafrontu@unam.mx (B.A. Frontana-Uribe).
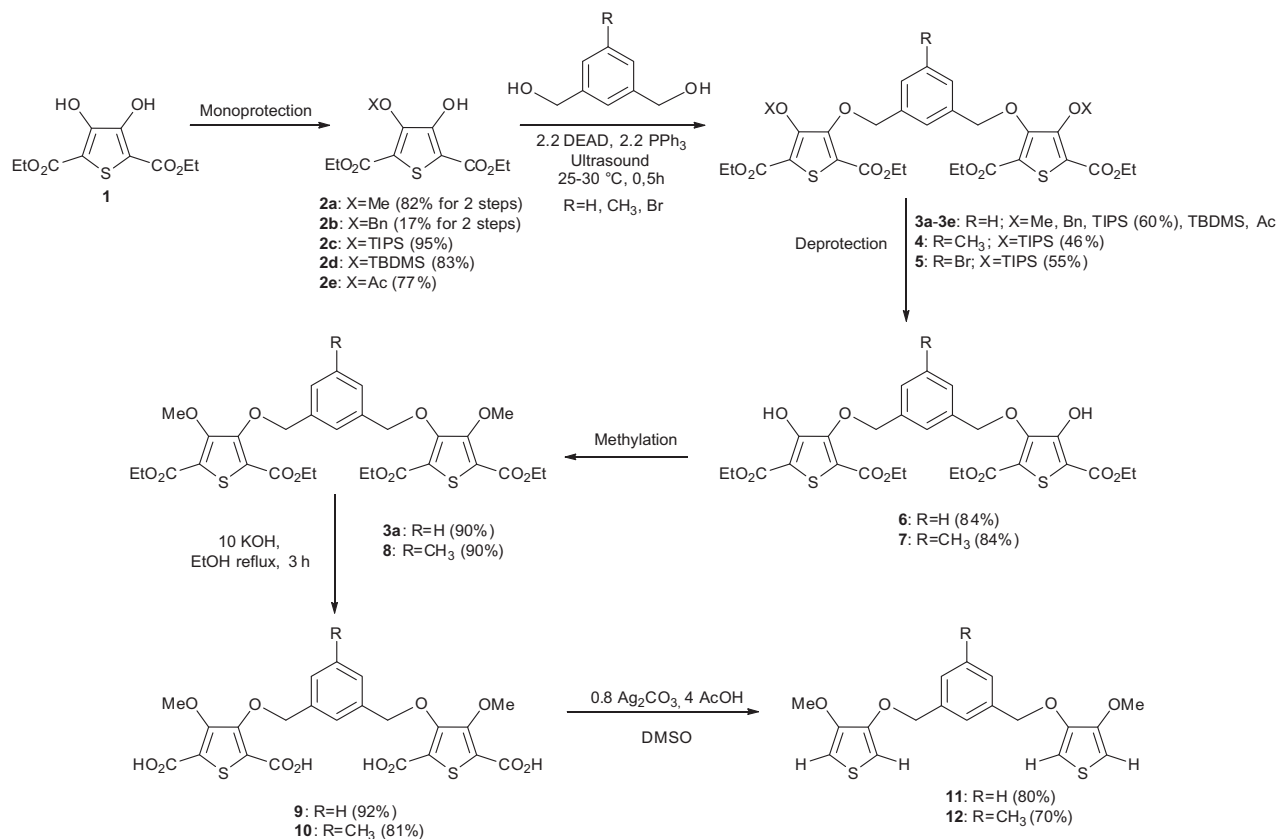
Scheme 1. Proposed synthetic pathway to prepare the *m*-xylene bridged bis-3,4 alkoxythiophenes asymmetrically substituted from compound **1**.

Table 1
m-Xylene bridge formation reaction to obtain **3a** via Williamson reaction
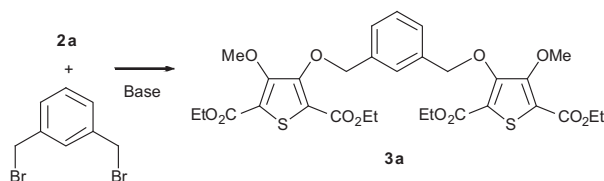
Entry	Base	Solvent	T (h)	T (°C)	% yield
1	NEt$_3$	DMF	20	90	9
2	NaH	DMF	2	90	15
3	NaH	DMF	72	90	15
4	NaH	DMF	90	90	5
5	NaH	DMF	0.25	150	21[a]
6	NaOH	Toluene/H$_2$O	18	100	15[b]

[a] Microwaves heating.
[b] Biphasic reaction, 10% mol TBABr was used as phase transfer compound.

2b showed an equivalent behavior. After these results the strategy for the coupling reaction was modified.

A 30% yield for **3a** was obtained, after using Mitsunobu methodology assisted by sonication (employed in the ether synthesis with steric hindered alcohols)[11] using the DEAD/PPh$_3$ system, **2a** and 1,3-bis(hydroxymethyl)benzene (entry 1, Table 2). Only 0.5 h were necessary to complete the reaction. No product was observed when the reaction was performed with the DIAD/P(*n*-Bu)$_3$ system, (entry 2, Table 2), therefore the mixture DEAD/PPh$_3$ was used for the preparation of the rest of bis-3,4-dialcoxythiophene systems. With the monobenzylated product **2b** a 11% yield of **3b** was obtained (entry 3, Table 2). The low reactivity of the monoalkylated

compounds in the two substitution process (Williamson and Mitsunobu) did not make them useful intermediaries in the preparation of bis-3,4-dialkoxythiophenes linked by an *m*-xylene bridge system.

Therefore, it was necessary to find a monoprotected high reactive intermediary to link the *m*-xylene bridge. Three easy-preparation monoprotected derivatives (**2c** X = TIPS, **2d** X = TBDMS and **2e** X = Ac, see Supplementary content for details of the synthesis) were tested with the Mitsunobu reaction only (entries 4–8, Table 2). These protective groups do not support the basic conditions of a Williamson reaction.[12] A 60% yield for double O-alkylation product **3c** was achieved from **2c** in smooth conditions

Table 2
m-Xylene bridge formation reaction to obtain **3a** via Mitsunobu reaction

2a–2e: X=Me, Bn, TIPS,TBDMS, Ac

3a–3e: R=H. X=Me, Bn, TIPS, TBDMS, Ac
4: R=CH$_3$. X=TIPS
5: R=Br. X=TIPS
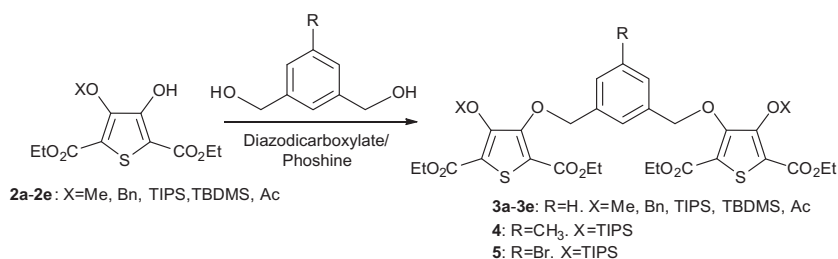
| Entry	R	X	Reagents	Solvent	T (°C)	Time (h)	% yield
1	H	Me	DEAD/PPh$_3$	THF	30	0.5	30
2	H	Me	DIAD/P(*n*-Bu)$_3$	THF	30	0.5	0
3	H	Bn	DEAD/PPh$_3$	THF	30	0.5	11
4	H	TIPS	DEAD/PPh$_3$	THF	30	0.5	60
5[a]	H	TIPS	DEAD/PPh$_3$	THF	30	16	13
6[a]	H	TIPS	DEAD/PPh$_3$	THF	60	16	32
7	H	TBDMS	DEAD/PPh$_3$	THF	30	0.5	37
8	H	Ac	DEAD/PPh$_3$	THF	30	0.5	26
9	CH$_3$	TIPS	DEAD/PPh$_3$	THF	30	0.5	46
10	Br	TIPS	DEAD/PPh$_3$	THF	30	0.5	55

20,000-Hz ultrasound equipment was used.
[a] Using conventional oil bath heating.

(30 °C and 0.5 h sonication entry 4, Table 2). The sonicated reaction was compared with one carried out using conventional oil bath heating; the latter resulted in longer reaction time and lower yield (entry 5, Table 2); higher temperature did not give better yields (entry 6, Table 2). The favorable effect of sonication on the rate of reaction was clear. In heterogeneous systems which imply ionic intermediaries (as Mitsunobu reaction) the mechanical effects of cavitation (i.e., size reduction and dispersion of reactants, improved mass transfer and increase of temperature)[13] seems to be favorable for our reaction. Lower yields were attained with the other monoprotected derivatives **2d** and **2e** under Mitsunobu conditions with sonication, 37% and 26% for **3d** and **3e**, respectively. Two additional compounds **4** and **5** were obtained from **2c** and two benzene substituted diols in 46% and 55% yields, (entries 9 and 10, Table 2). We observed that the reactivity of monoprotected molecules **2** in the Mitsunobu coupling reaction is dependent on the nature of the protecting group (Table 2). It has been reported that the reactivity in this reaction is correlated with the nucleophile acidity which protonates the zwitterionic adduct formed between the diazodicarboxylate and the phosphine.[14] In our case the TIPS derivative (**2c**) is the most acidic of the monoprotected molecules **2** and is therefore in agreement with the higher yield obtained in this Mitsunobu coupling reaction (60%). Three pathways for **3a** synthesis were compared (Scheme 2). The corresponding global yields were ∼25% from **2a**, 43% from **2c**, and 23% from **2d**. That the yield obtained from **2c** through a one step was higher than the one obtained through a shorter synthetic route was remarkable.

In both monoprotected esters **2** and esters linked with *m*-xylene bridge (**3**, **4**, and **5**) have characteristic ^{1}H NMR signals around 4.4–4.3 ppm corresponding to the CH$_2$ groups of the ethyl ester moieties. These changed their multiplicity from a quartet to a multiplet, when compared with the compound **1**. This change is due to the overlapping of both CH$_2$ signals provoked by the asymmetry introduced in the molecule by the protecting group. This was confirmed in the ^{13}C NMR spectra where two different carbonyl ester signals and two different methylene groups were observed in the ester compounds.

The route proposed in Scheme 1 was followed in order to complete the synthesis of bis-3,4-dialkoxythiophene linked by *m*-
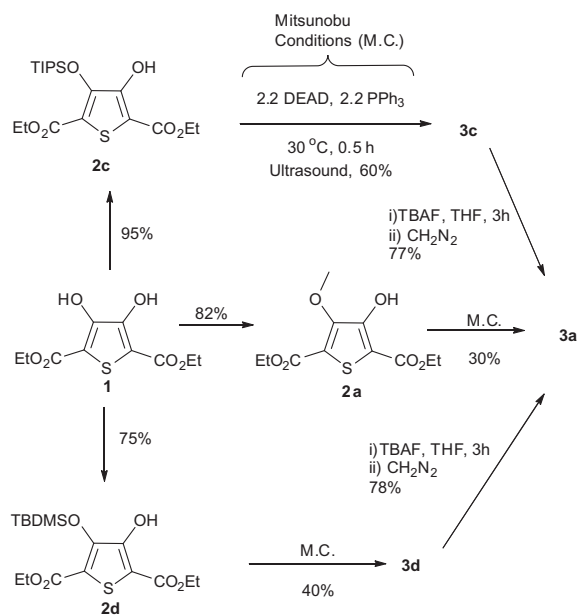
Scheme 2. Comparison of the synthetic approaches to obtain molecule **3a**.

xylene bridge systems. The deprotection of TIPS group was carried-out with NBu$_4$F to obtain **6** and **7** in similar yield (84%). The corresponding double methylation of these derivatives was performed by diazomethane offering a 90% yield for **3a** and **8**. The saponification reaction in refluxing ethanol[15] was applied to the bis-thiophenic derivatives **3a**, and **8** in yields of 92% for R = H and 81% for R = CH$_3$. The corresponding diacids **9** and **10** were submitted to protodecarboxylation reaction using a recently developed method,[16] catalyzed with Ag$_2$CO$_3$/AcOH system in DMSO using microwave heating, at 150 °C during and 15 min. Under these conditions yields of 80% for compound **11** (R = H), and 70% for compound **12** (R = CH$_3$) were obtained.

An average yield of 60% was obtained for both derivatives **11** and **12** when the last reaction was conducted in conventional
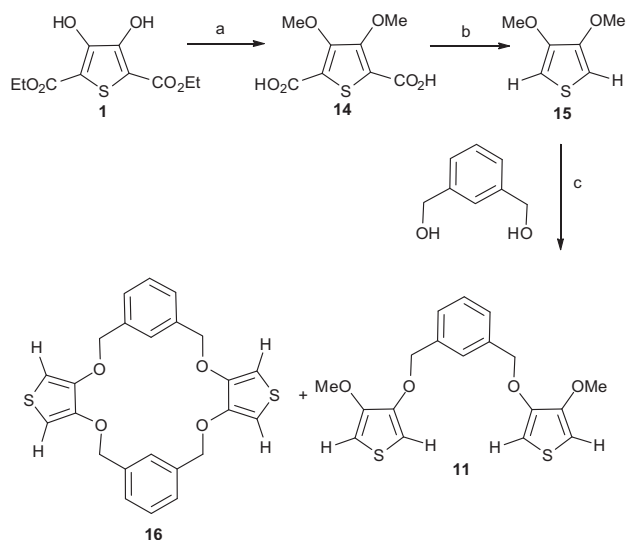
Scheme 3. Synthetic route to obtain 3,4-dimethoxythiophene **15**, and the target molecule **11**. Reagents and conditions: (a) (i) 10 CH$_2$N$_2$, DCM, 2 h; (ii) 10 KOH, EtOH reflux, 3 h; (iii) HCl, 74% for two steps. (b) 0.4 Ag$_2$CO$_3$, 2 AcOH, DMSO, μw at 150 °C 15 min, 82%. (c) PTSA, toluene.

heating at 120 °C during 16 h. An increase in the yield was observed when the reaction was carried out in microwave heating. The global yield of the six optimized steps from compound **1** is: 32% for **11** and 18% for **12**. For these molecules two signals in ^{1}H NMR were characteristic: the proton signals from the thiophene system at 6.2 ppm and the signal around 5.1 ppm corresponding to the methylene of the *m*-xylene bridge. In ^{13}C NMR the C–H of the thiophene ring was observed around 98–96 ppm and the signal corresponding to the methylene group of the *m*-xylene bridge was determined to occur at 72 ppm. This was confirmed in the ^{13}C NMR spectra where two different carbonyl ester signals and two different methylene groups were observed in the ester compounds.

The *trans*-etherification reaction was evaluated as an alternative to prepare the target molecule **11** from 3,4-dimetoxythiophene (**15**) and *m*-bis(hydroxymethyl)benzene. The dimethylated compound was prepared in a 61% global yield for three steps of reaction from **1** (Scheme 3). The protodecarboxylation reaction with Ag$_2$CO$_3$ and microwaves showed to be efficient and rapid. This method does not require the use of quinoline as a solvent, which is known to be a harmful and toxic substance and thus allows production of protodecarboxylation products in a cleaner way.[16]

In order to avoid a poly-transetherification reaction the synthesis of **11** was conducted in low concentrations of **15**. The first attempt with a 1:10 dilution provided **11** with 9% yield (entry 1, Table 3). When, the concentration of **15** was elevated two-fold, the yield increased to 40%. In addition, in these conditions the 18 member cycle (**16**) was isolated in 5% yield. Longer reaction time (entry 3, Table 3) did not improve the results. After a reaction of

96 h, the yield of **11** did not increase, the yield of compound **16** increased to 15%; the starting material (**15**) was completely degraded. Decreasing the reaction temperature to 70 °C did not show any advantage, probably due to the low diol solubility in toluene at this temperature, recovering part of the starting material (entry 4, Table 3).

The best global yield achieved when using a trans-etherification methodology to obtain compound **11** from thiophene **1** was 24%, which is 8% fewer than that obtained by the Mitsunobu methodology. Nevertheless, this route is 2 steps shorter and has fewer expensive intermediaries, which will render the method attractive when scaling-up the reaction.

It is noticed that via the other two methods compound **16** was not detected and with *trans*-etherification methodology ring closing reaction can be favored. A detailed study to favor the production of compound **16** using this method is necessary and will be reported in due time. Nevertheless, X-ray diffraction studies of compound **16** showed some interesting features that merit discussion (Fig. 1).[17] The central 18-membered macrocycle is formed by two alternating units of 1,3-bis(methoxy)benzene and two units of 3,4-dioxythiophene. The macrocycle has a structure similar to 18-crown-6, however due to carbons hybridization of thiophene group it adopts a nearly planar conformation, wherein the carbons C11 and C23 have the maximum deviation to the plane calculated for all the heterocycles with a distance of 0.165 Å and 0.147 Å, respectively (Table S6).

Only three X-ray structures with a heterocycle fragment that matches the situation of the aforementioned carbon atoms are reported in the literature[18] and in each of these cases the heterocycle adopts a quasi-planar conformation. In the unit cell, the molecules are arranged in zigzag form propagating in the [0 1 0] direction. The planes formed by the heterocycles have an interplanar distance of 3.257 Angstroms (Figs. S3 and S5) which is a clear
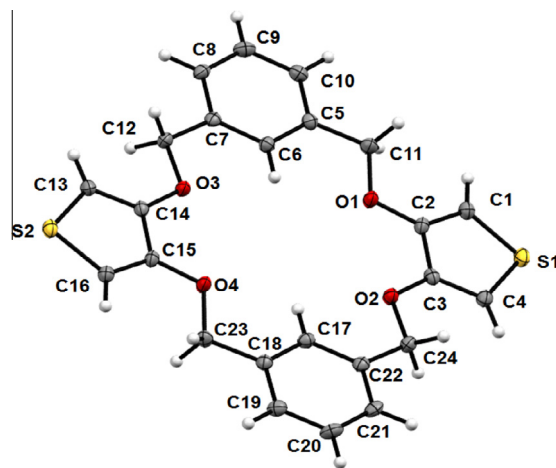
Figure 1. ORTEP Diagram at 50% of probability for compound **16**, the second positions was eliminated for better appreciation.

Table 3
Results of the formation of the *m*-xylene bridged compounds **11** and **16** via *trans*-etherification reaction

Entry	T (°C)	t (h)	Dilution[a]	% yield		
				11	**15**	**16**
1	110	60	1:10	9	23	—
2	110	48	1:5	40	20	5
3	110	96	1:5	38	—	15
4	70	96	1:5	17	60	—

[a] Dilution: mmol of compound **15** per mL toluene.

indication of a strong π–π interaction between the thiophene ring and the benzene moiety. The most characteristic signal in ^{1}H NMR was observed at 7.99 ppm corresponding to the aromatic protons of C6 and C17, which points inside of the 18 member heterocycle. ^{13}C NMR spectrum simplifies respect to compound **11**, due to the high symmetry of compound **16**.

Conclusion

Two asymmetric systems bis-3,4-dialcoxythiophenes bridged with a *m*-xylene moiety were synthesized in global yields of 18 and 32% through the O-alkylation synthetic route of six steps. Mitsunobu methodology was superior to Williamson reaction for the bridge construction. The selection of monoprotected derivative in the Mitsunobu reaction assisted by sonication is crucial in *m*-xylene bridge formation, with the TIPS protected derivative (**2c**) showing the highest yield. Also, a four step route based on trans-etherification of 3,4-dimethoxythiophene was developed, with similar yields and purity to construct the *m*-xylene bridge. The molecules **11**, **12**, and **16** may be used as building blocks in the preparation of π-conjugated materials. With exception of compound **16** these molecules are among the few examples reported of 3,4-dialcoxythiophenes containing different alkoxy substituents at these positions.

Acknowledgments

Supplementary data

Supplementary data (^{1}H, ^{13}C spectra as well as spectroscopic characteristics of the synthetized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.015.

References and notes

1. (a) Roncali, J.; Blanchard, P.; Frère, P. *J. Mater. Chem.* **2005**, *15*, 1589–1610; (b) Reeves, B. D.; Unur, E.; Ananthakrishnan, N.; Reynolds, J. R. *Macromolecules* **2007**, *40*, 5344–5352; (c) Mishra, A.; Ma, C. Q.; Bäuerle, P. *Chem. Rev.* **2009**, *109*, 1141–1276.
2. (a) Mauger, S. A.; Moulé, A. J. *Org. Electron.* **2011**, *12*, 1948–1956; (b) Yan, Q.; Zhou, Y.; Ni, B.; Ma, Y.; Wang, J.; Pei, J.; Cao, Y. *J. Org. Chem.* **2008**, *73*, 5328–5339; (c) Beaujuge, P. M.; Subbiah, J.; Choudhury, K. R.; Ellinger, S.; Mc Carley, T. D.; So, F.; Reynolds, J. R. *Chem. Mater.* **2010**, *22*, 2093–2106.
3. (a) Kumar, A.; Welsh, D. M.; Morvant, M. C.; Piroux, F.; Abboud, K. A.; Reynolds, J. R. *Chem. Mater.* **1998**, *10*, 896–902; (b) Welsh, D. M.; Kumar, A.; Meijer, E. W.; Reynolds, J. R. *Adv. Mater.* **1999**, *11*, 1379–1382; (c) Frontana-Uribe, B. A.; Heinze, J. *Tetrahedron Lett.* **2006**, *47*, 4635–4640; (d) Zong, K.; Madrigal, L.; Groenendaal, L. B.; Reynolds, J. R. *Chem. Commun.* **2002**. 2498-2489; (e) Caras-Quintero, D.; Bäuerle, P. *Chem. Commun.* **2002**, 2690–2691; (f) Xu, Z.; Kang, J. H.; Wang, F.; Paek, S. M.; Hwang, S. J.; Kim, Y.; Kim, S. J.; Choy, H. J.; Yoon, J. *Tetrahedron Lett.* **2011**, *52*, 2823–2825; (g) Harris, C. S.; Germain, H.; Pasquet, G. *Tetrahedron Lett* **2008**, *49*, 5946–5949.
4. (a) Merz, A.; Rehm, C. *J. Prakt. Chem.* **1996**, *338*, 672–674; (b) von Kieseritzky, F.; Allared, F.; Dahlstedt, E.; Hellberg, J. *Tetrahedron Lett.* **2004**, *45*, 6049–6050.
5. (a) Agarwal, N.; Mishra, S. P.; Kumar, A.; Hungb, C. H.; Ravikanth, M. *Chem. Commun.* **2002**, 2642–2643; (b) Caras-Quintero, D.; Bäuerle, P. *Chem. Commun.* **2004**, 926–927; (c) Roquet, S.; Leriche, P.; Perepichka, I.; Jousselme, B.; Levillain, E.; Frère, P.; Roncali, J. *J. Mater. Chem.* **2004**, *14*, 1396–1400.
6. Gronowitz, S.; Hörnfeldt, A.-B. *Thiophenes*; Academic Press: London, 2004; pp 577–598.
7. (a) Corral, C.; El-Ashmawy, M. B.; Lissavetzky, J.; Basilio, A.; Giraldez, A. *Eur. J. Med. Chem.* **1987**, *22*, 251–254; (b) Corral, C.; El-Ashmawy, M. B.; Lissavetzky, J.; Bravo, L.; Darias, V.; Martin, D. *Il Farmaco* **1987**, *42*, 267–275.
8. Furuta, P.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2003**, *125*, 13173–13181.
9. (a) Castillo, R.; Izquierdo, M. L.; Alvarez-Builla, J. *Tetrahedron Lett.* **2008**, *48*, 5899–5903; (b) Patrick, D. A.; Bakunov, S. A.; Bakunova, S. M.; Kumar, E. V.; Chen, H.; Jones, S. K.; Wenzler, T.; Barzcz, T.; Werbovetz, K. A.; Brun, R.; Tidwell, R. R. *Eur. J. Med. Chem.* **2009**, *44*, 3543–3551.
10. Sarju, J.; Danks, T. N.; Wagner, G. *Tetrahedron Lett.* **2004**, *45*, 7675–7677.
11. Lepore, S. D.; He, Y. J. *J. Org. Chem.* **2003**, *68*, 8261–8263.
12. Kocienski, P. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2005. ch. 4, pp. 199–223, 241–257, 323–330.
13. Mason, T. J. *Chem. Soc. Rev.* **1997**, *26*, 443–451.
14. Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551–2651.
15. Coffey, M.; McKellar, B. R.; Reinhardt, B. A.; Nojakowski, T.; Feld, W. A. *Synth. Commun.* **1996**, *26*, 2205–2212.
16. Cisneros-Pérez, P. A.; Martínez-Otero, D.; Cuevas-Yáñez, E.; Uribe-Frontana, B. A. *Synth. Commun.* **2014**, *44*, 222–230.
17. CDCC number: 1046649 (Compound **16**).
18. (a) Grochowski, J.; Rys, B.; Serda, P.; Wagner, U. *Tetrahedron: Asymmetry* **1995**, *6*, 2059–2066; (b) Amouri, H.; Besace, Y.; Vaissermann, J. *C. R. Chim.* **2003**, *6*, 193–197; (c) Ferguson, G.; Ruhl, B. L.; McKervey, M. A.; Browne, C. M. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1992**, *48*, 2262–2264.