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Improved synthesis of a quaterthiophene-triazine-diamine derivative, a promising molecule to study pathogenic prion proteins

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ABSTRACT

The 6,6′-([2,2′:5′,2″:5″,2‴-quaterthiophene]-5,5‴-diyl)bis(1,3,5-triazine-2,4-diamine) (MR100), has been previously investigated in our research group through its biological activities toward pathogenic prion proteins (PrP^{Sc}). This compound presents a high affinity to protein strains and interacts selectively with at least one β-sheet rich isoform of prion protein. Herein we present the improved total synthesis of MR100, through a palladium-catalyzed direct double arylation using the concerted metalation deprotonation mechanism (CMD).

Introduction

Prion diseases are fatal neurodegenerative conditions characterized by the accumulation of PrP Scrapie isoforms (PrP^{Sc}) in the brain tissues of many mammalian including humans.[1] The transmissible subacute spongiform encephalopathies (TSSEs) cause death in 100% of the cases by neurological damage and have received a remarkable development since the mad cow crisis in 1986. The appearance of the new variant of Creutzfeldt-Jakob disease (vCJD) in humans in 1996 has reinforced the interest to develop new routes to identify and to treat prion diseases.[2] However, at the current time, no available treatment exists for patients suffering from TSSEs, nor is there a selective test for earlier diagnosis.[3] The cellular protease resistant protein (PrP^{C}) and the scrapie protease resistant protein (PrP^{Sc}) are isoforms and present identical primary structures due the same amino acid sequences. They differ only in terms of their secondary and tertiary structures where PrP^{Sc} has a higher content of β-pleated sheets and PrP^{C} has a greater number of alpha helices.

The mechanism of the propagation of the disease remains obscure at this stage but it is consistent with an autocatalytic, templated, or seeded polymerization of PrP^{Sc} isoforms.[4] The progress in the mechanism understanding and the synthesis of new molecules having a high selectivity with the β-sheet rich PrP^{Sc} isoforms could afford a new option in the early diagnosis of prion diseases enhancing the survival chances of patients.

However, studies of this mechanism and new molecules applied in the diagnosis of prion diseases having PrP^{Sc} selectivity are limited. Prusiner's research group have done pioneering studies exploring therapeutic candidates using persistently prion-infected cells.[5] He has been awarded with the Nobel Prize in Physiology or Medicine in 1997 for his discovery of prions as a new biological principle of infection. Caughey and co-workers demonstrated that congo red and sulfated polyanions could partially inhibit PrP^{Sc} formation in prion-infected cell cultures.[6] Kuwata and co-workers have described the affinity of GN8 with PrP^{C} doing many studies with this compound in the selective interactions with the cellular prion protein.[7]

The 6,6′-([2,2′:5′,2″:5″,2‴-quaterthiophene]-5,5‴-diyl)bis(1,3,5-triazine-2,4-diamine) (MR100) has been investigated in our research group through its selective activity with PrP^{Sc} isoforms.[8] In vitro screenings on cell cultures chronically infected with prions were performed with MR100 using murine neuroblastoma lines chronically infected with prion strains (scrapie strain stabilized in mice). The infected cells were incubated with solutions of

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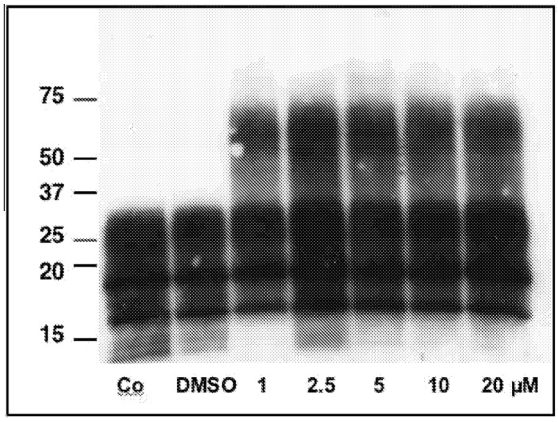


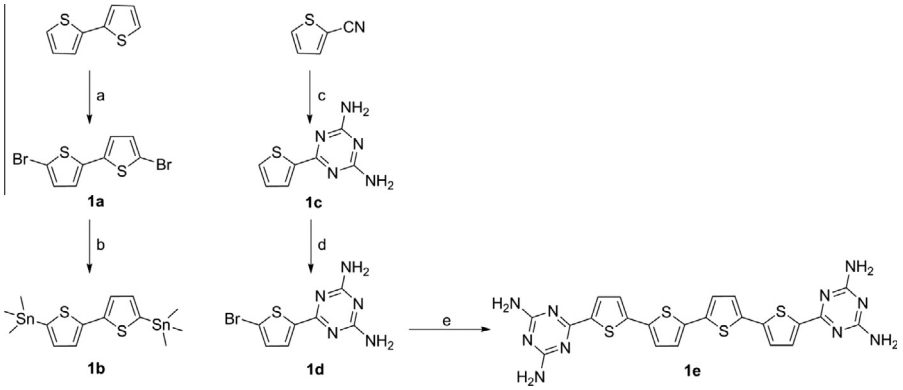
Figure 1. Western blot showing the oligomerization of PrP^{Sc} (monomer) (27–30) kDa giving PrP^{Sc} ~60 kDa (dimmer) after incubation with MR100 at different concentrations. Co = control where no MR100 has been used and DMSO = cells incubated only with 5% of DMSO in water.

MR100 H_2O/DMSO 5:95 (v/v), at different concentrations from 1 to 20 μM, for a period of 3 days at 37 °C and 5% CO_2 giving positive results to the oligomerization of PrP^{Sc}. In Figure 1, Co represents the control cells without treatment with MR100 and DMSO the cells only treated with 5% DMSO in water. From these results, it appears that the effect of oligomerization is very important since for doses of 1 μM the saturation of the signal is achieved. MR100 presents a high affinity to protein strains and interacts selectively with at least one β-sheet rich isoform of prion.

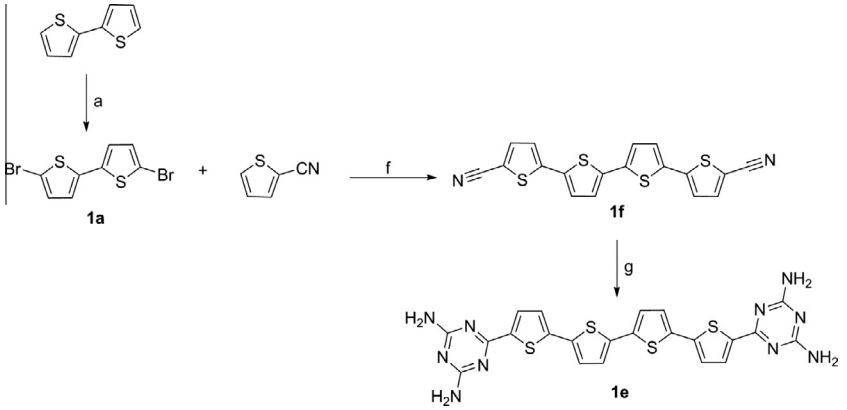
MR100 has been firstly synthesized using a five step protocol where a Stille cross-coupling reaction was used in the main step of the synthesis (Scheme 1). The double C—C bond formation between the 5,5′-bis(trimethylstannyl)-2,2′-bithiophene (**1b**) and two equivalents of the 6-(5-bromothiophen-2-yl)-1,3,5-triazine-2,4-diamine (**1d**) precursor have been accomplished with a palladium(0) catalyst affording the desired product MR100 (**1e**).[8]

The Stille cross-coupling presents some drawbacks in terms of biological applications mostly related with the use of toxic triorganotin precursors.[9] The biocide activities and the possible neurological damage associated with stannanes led us to its total elimination from the synthesis of MR100.[10] Besides its toxicity the purifications associated with this process also require long time consuming preparations and specific conditions to avoid drug degradation.

The new pathway avoiding organometallic precursors was developed thinking in new methodologies more adapted to biological applications. We have investigated a direct double C—H arylation as a helpful tool in the main step of the synthesis of MR100 (**1e**).[11] Since works of Ohta and co-workers,[12] reporting in 1990 the direct 2- or 5-arylation of several heteroaromatics with aryl halides via a C—H bond activation proceed using $Pd(PPh_3)_4$ as the catalyst, some examples of thiophene C—H arylation have been reported.[13] Lemaire and co-workers have proposed another catalytic version of this reaction using cyanothiophenes with $Pd(OAc)_2$/Bu_4NBr/K_2CO_3 as the catalytic system, affording the 2-cyano-5-phenylthiophene in good yields.[14] Doucet et al. developed a large scope of direct 3-, 4- or 5-arylation of C5-heteroaromatic compounds catalyzed by Pd.[15] Fagnou and co-workers have reported



Scheme 1. Stille cross-coupling pathway (5 steps): (a) NBS, $CH_3COOH/CHCl_3$, rt, 4 h, 98%; (b) *n*BuLi, THF, −40 °C, 2 h/Me_3SnCl; THF, rt, 3 h, 98%; (c) 2-cyanoguanidine, KOH, DMSO, 80 °C, 16 h, 89%; (d) NBS, CH_3COOH, rt, 48 h, 90%; (e) $Pd(PPh_3)_3$, pyridine/DMF, 110 °C, 16 h, 62%.



Scheme 2. New synthetic approach to MR100 (3 steps): (a) NBS, $CH_3COOH/CHCl_3$, 70 °C, 4 h, 98%; (f) $Pd(PPh_3)_4$, PivOH, K_2CO_3, toluene/DMA 1:1 (v/v), 110 °C, 48 h, 72%; (g) 2-cyanoguanidine, KOH, DMSO, 80 °C, 16 h, 91%.

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Table 1
Catalytic tries in the synthesis of **1f** under different solvent and temperature conditions

Entry	Ar–X_n	Ar–H	mol % $Pd(PPh_3)_4$	K_2CO_3	Co-catalyst	Solvent (v/v)	80 °C	90 °C	110 °C	Yield %
1	T_2Br_2	T_1CN	6%	1.5 equiv	No	DMF	19 h	19 h	19 h	0
2						DMA				0
3						1,4-Dioxane				0
4						toluene				0
5						DMA/toluene 1:1				0
6						DMA/THF 1:1				0

Experimental conditions: **1a** (1 equiv), thiophene-2-carbonitrile (6 equiv), (1.5 equiv) K_2CO_3, no co-catalyst, DMA/Toluene 1:1 (v/v), 110 °C, C: 0.23 M based on **1a** initial amounts.

Table 2
Optimization of the catalytic conditions

Entry	mol % $Pd(PPh_3)_4$	Co-catalyst	Co-catalyst[a] (pK_a)	Equiv K_2CO_3	Yield[b] %
7	0	0.3 equiv pivalic acid	5.03	1.5	0
8	6	0.3 equiv pivalic acid	5.03	1.5	58
9	6	0.6 equiv pivalic acid	5.03	1.5	34
10	6	1.2 equiv pivalic acid	5.03	1.5	27
11	6	1.8 equiv pivalic acid	5.03	1.5	33
12	6	0.3 equiv benzoic acid	4.21	1.5	9
13	6	0.3 equiv pyridine	5.22	1.5	8
14	6	0.3 equiv phenyl phosphonic acid	2.0; 6.7	1.5	<1
15	6	0.3 equiv histidine	1.7; 6.04; 9.09	1.5	0
16	6	0.3 equiv pyrrolidine	11.27	1.5	0
17	2	0.3 equiv pivalic acid	5.03	1.5	46
18	8	0.3 equiv pivalic acid	5.03	1.5	20
19	12	0.3 equiv pivalic acid	5.03	1.5	23
20	16	0.3 equiv pivalic acid	5.04	1.5	36
21	6	0.3 equiv pivalic acid	5.03	3	27
22	8	0.3 equiv pivalic acid	5.03	3	72
23	16	0.3 equiv pivalic acid	5.03	3	16
24	24	0.3 equiv pivalic acid	5.03	3	22

[a] See Ref 18.
[b] Yields of isolated product in mol %. Catalytic conditions: **1a** (1 equiv), thiophene-2-carbonitrile (6 equiv), K_2CO_3, co-catalyst, DMA/Toluene 1:1 (v/v), 110 °C, 48 h, C: 0.23 M. All reactants have been calculated based on **1a** initial amounts.

Table 3
One pot catalytic tries using $Pd(OAc)_2$/(4 equiv)PPh_3 catalyst

Entry	mol % $Pd(OAc)_2$/(4 equiv)PPh_3	Co-catalyst (0.3 equiv)	Co-catalyst (pK_a)	Salt (1.5 equiv)	Time	Yield[a] %
25	6	Pivalic acid	5.03	K_2CO_3		38
26	6	Pivalic acid	5.03	KI		0
27	6	Pivalic acid	5.03	$K_2C_2O_2$[b]		0
28	6	Propionic acid	4.87	K_2CO_3	22 h	10
29	6	Hexanoic acid	4.88	K_2CO_3		11
30	6	Octanoic acid	4.89	K_2CO_3		9
31	6	Pivalic acid	5.03	K_3PO_4		13

[a] Yields of isolated product in mol %.
[b] Potassium oxalate. Catalytic conditions: **1a** (1 equiv), thiophene-2-carbonitrile (6 equiv), salt (1.5 equiv), co-catalyst (0.3 equiv), DMA/Toluene 1:1 (v/v), 110 °C, 22 h, C: 0.23 M based on **1a** initial amounts.

examples of palladium-catalyzed direct arylation using a concerted metalation deprotonation (CMD) pathway with thiophenes.[16] Pivalic acid was used as a proton shuttle which works as a helpful tool increasing the reaction yields. The CMD mechanism predicts relative reactivity and regioselectivity for a diverse set of arenes.[17] Aryl–aryl cross-couplings can be regioselectively favored using electron deficient aromatics as for example aryl-nitriles and aryl-nitro compounds. The cross-couplings are directly influenced by the presence of the electron-withdrawing groups leaving the aromatic ring more reactive. In our case this methodology has been applied to selectively couple substituted thiophenes.

Those methodologies can be easily applied at both laboratory and industrial scale on a broad range of electron poor aryl or heteroaryl derivatives but in this work we focus on the synthesis of MR100 due to its biological applications in prion protein identification.

Results and discussion

With the new procedure MR100 can be obtained in three steps (Scheme 2) where the CMD mechanism is applied in step 2 between the dibrominated compound (**1a**) and 2-thiophenecarbonitrile. The final step of the synthesis is achieved by cycloaddition between (**1f**) and 2-cyanoguanidine.

A first screening of the experimental conditions was performed. The C—H arylation (step **f**) was monitored by TLC and UV, and was stopped when no more reactivity was observed (around 19 h). In the presence of $Pd(PPh_3)_4$ (tetrakis(triphenylphosphine)palladium(0)) and K_2CO_3, no conversion into product (**1f**) was observed when no pivalic acid was used as the co-catalyst whatever the temperature between 80 and 110 °C (Table 1). The co-catalyst seems to play a major role in the deprotonation of 2-thiophenecarbonitrile favorising the CMD mechanism.

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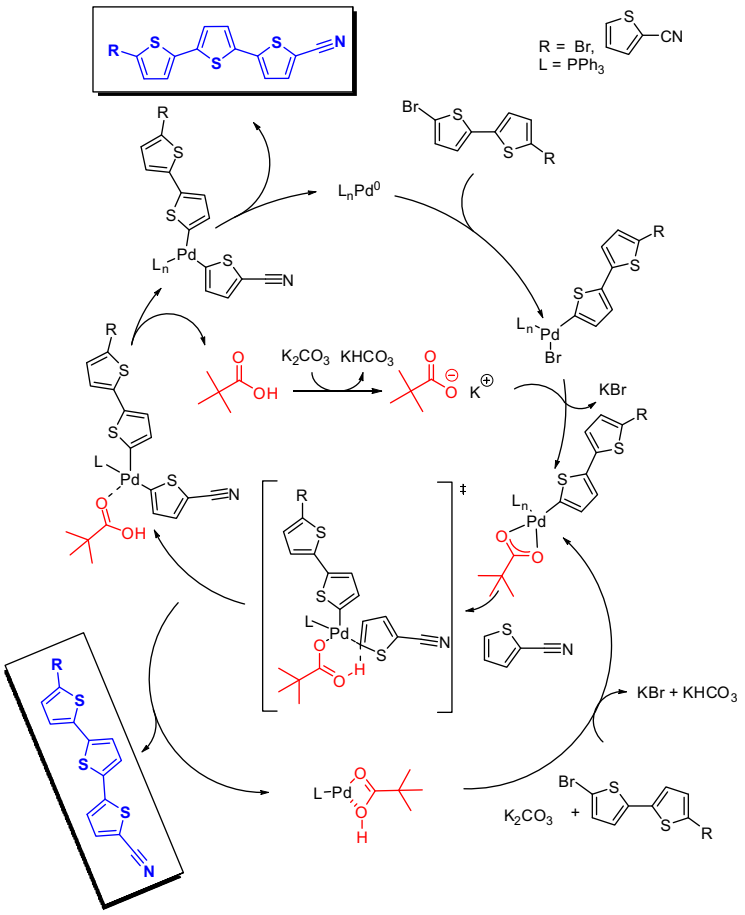

Scheme 3. Proposed mechanism using the CMD pathway.

Only partial solubility of all starting reagents has been observed in pure 1,4-dioxane and toluene. The DMA/Toluene 1:1 (v/v) solvent mixture provided a better solubility at 110 °C and has been chosen as standard conditions for the following tries.

Optimization of the synthetic conditions of 1f

When no $Pd(PPh_3)_4$ catalyst was applied (entry **7**) no conversion into product **1f** was observed confirming the necessity of palladium species to promote the catalytic coupling. When 0.3 equiv of pivalic acid was added (entry **8**) the diarylated compound (**1f**) was isolated as the major product in 58% yield. Increasing the amounts of pivalic acid (entries **9**–**11**) did not improve the yields of the diarylated compound. The catalytic CMD mechanism using pivalic acid as the proton shuttle seems to have a saturation point around 0.3 equiv under our conditions.

When changing the co-catalyst by benzoic acid (**12**), pyridine (**13**), phenyl phosphoric acid (**14**) lower yields were obtained compared to pivalic acid results. With higher and lower co-catalyst pK_a values[18] (entries **15** and **16** respectively) no conversions into products were achieved suggesting that there is a narrow interval where the reactivity of the co-catalyst is optimal. This interval seems to be around $pK_a = 4–5$ where pivalic acid gave good conversions and benzoic acid, pyridine (entries **12** and **13**) gave lower yields.

There is no doubt about the improvement generated by pivalic acid in the system although no rationalization can be done in terms of pK_a influence using exclusively this parameter. When decreasing the amount of $Pd(PPh_3)_4$ catalyst to 2 mol % (entry 17) maintaining the amount of K_2CO_3 at 1.5 equiv we did not observe an improvement in terms of isolated product **1f**. When the amounts of $Pd(PPh_3)_4$ were increased (entries **18**–**20**) to 8, 12, and 16 mol % we observed a decrease in the isolated yield due to an increased formation of palladium black in the catalytic system.

The effect of the alkalinity based on the amount of K_2CO_3 present in the catalytic system was studied for different concentrations of catalyst $Pd(PPh_3)_4$ (entries **21**–**24**). The objective was to verify if higher amounts of K_2CO_3 could promote a faster formation of pivalate anions promoting in this way the CMD mechanism. Indeed with 8 mol % $(PdPPh_3)_4$/3 equiv K_2CO_3/(0.3 equiv) pivalic acid (entry **22**) the diarylated product (**1f**) was isolated with a yield of 72%. Finally, under the same conditions, we substituted the K_2CO_3 base by potassium or caesium acetate in order to see if the yield was increased. In fact, whatever the salt used, yields are always lower than with K_2CO_3 (SI: Table SI1).

We also studied a one pot synthesis involving $Pd(OAc)_2$/(4 equiv)PPh_3 as another palladium(0) catalyst. In this system, the best yield (entry 25, 38%) was obtained when applying 6 mol % of $Pd(OAc)_2$/(4 equiv)PPh_3 catalyst, 1.5 equiv K_2CO_3, (0.3 equiv) pivalic acid, 22 h. The lower yields could be explained by the slower in situ formation of $Pd(PPh_3)_3$ catalyst and the presence of the acetate anions providing an increased ionic strength in the system and generating a competition with pivalic acid.[19] When applying another source of potassium salts such as KI and $K_2C_2O_2$ (potassium oxalate) (entries **26** and **27**, respectively) no conversion into product **1f** was observed (Table 3). These results confirmed the necessity of basic species in the catalytic system to promote the in situ deprotonation of pivalic acid into the pivalate anion, favoring the CMD mechanism. The entries **28**–**30** using other sources of co-catalysts such as propionic, hexanoic, and octanoic

acids gave low yields and could confirm the narrow interval of pK_a of the co-catalyst mentioned above (Table 2) to promote the C—C bond formation in this synthesis.

CMD Proposed mechanism

The proposed CMD mechanism has been used to predict the reactivity and the regioselectivity between the electron deficient 2-thiophenecarbonitrile and 2,2′-dibromobithiophene.[20] The plausible transition state (TS) involving both substrates and the proposed mechanism is shown in Scheme 3.

In our case the TS is the one where the pivalate anion assists the deprotonation of the π-rich 2-thiophenecarbonitrile in C5 position favorising its oxidative addition on palladium catalyst.

The final step in the synthesis of MR100 was achieved by cycloaddition of **1f** with dicyandiamide. The reaction was performed in DMSO at 80 °C with KOH. Compound **1e** was recrystallized from water at 80 °C during 15 min and filtrated over celite to eliminate the remaining dicyandiamide. The crude was purified by thin layer chromatography (TLC), after several unsuccessful attempts by flash chromatography techniques, giving a pure dark-red compound (**1e**) in 91% yield. The extremely polar character of MR100 is a great asset to its biological activity but represents an inopportune characteristic for its purification.[21–23]

Conclusion

The double direct arylation using the CMD mechanism has been achieved between the commercially available 2-thiophenecarbonitrile and the dibrominated compound (**1a**) as the main step toward the synthesis of 6,6′-([2,2′:5′,2″:5″,2‴-quaterthiophene]-5,5‴-diyl)bis(1,3,5-triazine-2,4-diamine) (MR100). The improved protocol involving tetrakis(triphenylphosphine)palladium(0) as the catalyst, pivalic acid, and an excess of K_2CO_3 to form the pivalate anion in situ, led to the synthesis of MR100 **(1e)**. An overall yield of 64% has been obtained and the time needed for the synthesis of MR100 was drastically reduced.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.098.

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21. *Procedure for the synthesis of 5,5′-dibromo-2,2′-bithiophene* **1a**: A mixture of 2,2′-bithiophene (5.40 g, 32.4 mmol) and NBS (11.57 g, 64.8 mmol, 2 equiv) in a solvent mixture $CHCl_3$/acetic acid 100% (1:1 (v/v), 300 mL) was stirred at 70 °C for 4 h. The reaction media was diluted with CH_2Cl_2 (50 mL) and a saturated aqueous solution of Na_2CO_3 (100 mL). The organic phase was isolated and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were assembled, dried with $MgSO_4$, filtered and evaporated to give a pale yellow solid that was then washed with acetone giving the pure product **1a** (10.42 g, 98%). Recrystallization from THF afforded a highly pure product. ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): 7.23–7.22 (d, J = 3.9 Hz, 2H), 7.15–7.14 (d, J = 3.9 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 136.86, 131.60, 125.22, 110.84. MS(ESI+): m/z = 324.05. UV–visible (DMSO) λ_{max} = 325 nm. IR(ATR): 3069 cm^{-1} (Ar–H)$_{str}$; 1683 cm^{-1} (C=C conjugated)$_{str}$; 1416 cm^{-1} (R_1-C=C-R_2 *cis*)$_{str}$; 1293 cm^{-1} (C=C)$_{bending}$. Elemental analysis: calculated: C 29.65; H 1.24; S 19.79; found: C 30.03; H 1.40; S 18.13.
22. *Procedure for the synthesis of [2,2′:5′,2″:5″,2‴-quaterthiophene]-5,5‴-dicarbonitrile* **1f**: A mixture of **1a** (745 mg, 2.30 mmol), 2-thiophenecarbonitrile (1.28 mL, 13.7 mmol, 6 equiv), K_2CO_3 (950 mg, 6.87 mmol, 3 equiv), pivalic acid (77.7 μL, 0.69 mmol, 0. 3 equiv) and $Pd(PPh_3)_4$ (212 mg, 0.18 mmol, 0.08 equiv) in a solvent mixture of anhydrous toluene/DMA (1:1 (v/v), 10 mL) was stirred under argon atmosphere at 110 °C for 48 h. The reaction mixture was diluted with toluene (50 mL), filtered over celite and the solvent was evaporated in vacuo. The crude was purified by precipitation from toluene (3 times) giving **1f** (629 mg, 72%) which was used without any further purification to the next step. ^{1}H NMR at 40 °C (DMSO-d_6, 600 MHz) δ (ppm): 7.95–7.94 (d, J = 3.8 Hz, 2H), 7.57–7.56 (d, J = 3.8 Hz, 2H), 7.52–7.51 (d, J = 3.8 Hz, 2H), 7.47–7.46 (d, J = 3.8 Hz, 2H). ^{13}C NMR at 40 °C (DMSO-d_6, 150 MHz) δ (ppm): 143.09, 140.11, 136.62, 133.42, 128.05, 126.25, 124.76, 113.93, 106.32. MS(ESI+): m/z = 379.8. UV–Visible (DMSO) λ_{max} = 424 nm. IR(ATR): 3094 cm^{-1} (Ar–H)$_{str}$, 2215 cm^{-1} (Ar–CN)$_{str}$, 1446 cm^{-1} (C=C)$_{bending}$, 852 cm^{-1} (R_1CH=CR_2R_3)$_{str}$. Elemental analysis: calculated: C 56.82; H 2.12; N 7.36; S 33.70; found: C 56.95; H 1.97; N 6.83; S 31.71.
23. *Procedure for the synthesis of 6,6′-([2,2′:5′,2″:5″,2‴-quaterthiophene]-5,5‴-diyl)bis(1,3,5-triazine-2,4-diamine)* **1e**: A mixture of **1f** (366 mg, 0.96 mmol), dicyandiamide (483 mg, 5.74 mmol, 6 equiv), and KOH (113 mg, 2.02 mmol, 2.1 equiv) in DMSO (10 mL) was stirred at 80 °C for 16 h. Distilled water

(100 mL) was added and the crude was recrystallized at 80 °C during 15 min. The red precipitate was hot filtrated over celite, washed with acetonitrile (50 mL) and purified by thin layer chromatography (TLC) to give 481 mg (91%) of **1e**. TLC Purification: The crude was solubilized in the minimum amount of DMSO and spotted on TLC plaques. The plaques were oven dried at 190 °C during 3 min and eluted using DCM/MeOH 9:1 (v/v). The separated spots were extracted from the TLC plaques with DMF, filtrated over celite, and evaporated. The product was dissolved in methanol (50 mL) at room temperature, filtered, and dried giving 481 mg (91%) of a dark red pure product **1e**. ^{1}H NMR (DMSO-d_6, 600 MHz) δ (ppm): 7.75 (d, J = 3.81 Hz, 2H), 7.42 (d, J = 3.81 Hz, 2H), 7.39–7.38 (m, J = 6.74 Hz, 4H), 6.77 (s, 8H, –NH_2). ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm): 166.9, 166.1, 141.7, 139.3, 135.5, 135.4, 129.7, 126.0, 125.7, 124.9. HRMS(ESI+): m/z = 549,0527. UV–Visible (DMSO) λ_{max} = 439 nm. IR (ATR): 3324 cm^{-1} $(-NH_2)_{str}$, 3153 cm^{-1} $(N-H)_{str}$, 1622 cm^{-1} $(C{=}C$ conjugated$)_{str}$, 1524 cm^{-1} $(NH\text{-}C)_{bending}$, 1429 cm^{-1} $(C{=}C)_{str}$, 1386 cm^{-1} $(R_1\text{-}C{=}C\text{-}R_2)_{str}$, 848 cm^{-1} $(R_1CH{=}CR_2R_3)_{str}$. Elemental analysis: calculated: C 48.16; H 2.94; N 25.53; S 23.37; found: C 47.43; H 2.74; N 22.20; S 22.53.