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Microwave-activated synthesis of thiazolo[5,4-*d*]-thiazoles by a condensation/oxidation sequence†‡

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A microwave-assisted preparation of symmetrical thiazolo[5,4-*d*]thiazoles from the corresponding aldehydes is presented. The two-step reaction sequence comprises the condensation of aldehydes with dithiooxamide followed by oxidation/aromatization with 1,4-benzoquinone derivatives. The new procedure provides the desired products in good yields and in most cases allows reduction of the excess of aldehyde employed in the process compared to previous methodologies. For the first time, application of the reaction both on aromatic and aliphatic aldehydes is demonstrated.

Introduction

Thiazole derivatives, either of natural or synthetic origin, are known to possess a range of interesting properties: for example, the thiazole ring is present in thiopeptide antibiotics,[1] and some natural thiazole-containing macrocycles have shown cytotoxic and antimicrobial activities.[2] In addition, they have found use in materials science since they exhibit strong fluorescence[3] as well as non-linear optical[4] and semiconducting properties.[5]

Among thiazole derivatives, thiazolo[5,4-*d*]thiazoles (**1**) are a class of compounds characterized by a rigid and coplanar bicyclic scaffold giving rise to an extended π-electron system (Fig 1).[6] These substances were also initially investigated for their potential biological activity,[7] but recently the interest in their properties has increased spectacularly due to their inclusion in functional materials with several applications. In particular, they have been used as spacer units in semiconducting materials for polymer and organic light-emitting diodes,[8] organic field-effect transistors,[9] as well as fluorescent sensors and emitters.[10] Moreover, they have been incorporated in donor/acceptor polymers for organic bulk heterojunction solar cells,[11] and introduced in organic sensitizers for dye-sensitized solar cells.[12] Finally, thiazolo[5,4-*d*]thiazoles might represent an innovative class of ligands for coordination chemistry.[13]

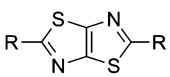

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Fig. 1 The thiazolo[5,4-*d*]thiazole ring system.

The first compound of this class was prepared in 1891 by Ephraim,[14] but its correct structure was established only in 1960 by Johnson *et al.*,[15] who were the first to prepare a large number of analogues.[16] These were obtained by reaction of dithiooxamide with an excess of the appropriate aromatic aldehydes, a reaction which was often affected by some limitations, such as high temperatures, long reaction times, large excess of aldehyde required and, frequently, low to moderate yields.[8–11,13,15,16] A few alternative synthetic procedures have been reported based on the stepwise elaboration of different starting materials.[6,17–20] More recently, milder conditions for the condensation of dithiooxamide with aldehydes have been described,[21] however, a systematic study to find optimal and more general conditions, tolerant to different functional groups, has not been reported so far.

The advent of microwave-assisted organic synthesis has contributed significantly to the development of mild and sustainable procedures for the preparation of organic compounds as it often leads to a remarkable decrease in reaction times and chemical waste, an increase in yields, and an easier product workup.[22] This technique has also found useful application in the synthesis of heterocycles,[23] which led us to think it could also be exploited for thiazolothiazole synthesis. Indeed, during our studies on the preparation of new organic

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† This paper is dedicated to the memory of Prof. Alessandro Degl'Innocenti.

‡ Electronic Supplementary Information (ESI) available: Copies of ^{1}H-and ^{13}C-NMR spectra of compounds **1b**, **1c**, **1d**, **1e**, **1f**, **1i**, **1j**, **1k**, **1l**, **1m**, **1o**, **1p**, **1q**, **1r**, **4**, ^{1}H-NMR spectrum of compound **1n**, ^{1}H-NMR spectrum of the crude **1b**/**3** mixture. See DOI: 10.1039/c3ra45015e

sensitizers for dye-sensitized solar cells,[12a,c] we observed that the yield of thiazolo[5,4-*d*]thiazole **1a**, stemming from aldehyde **2a** (Scheme 1), could be significantly enhanced if the reaction was carried out in solvent-free conditions and under MW-irradiation. Thus, the efficiency of the reaction was improved compared to the usual thermal process;[8a] moreover, the reaction time was notably shortened to just 15 minutes.[24]

Prompted by this result and in consideration of the demonstrated utility of thiazolo[5,4-*d*]thiazoles, we decided to study in more detail the effect of microwave activation in the condensation of dithioxoamide with aromatic aldehydes, aiming to find a general and mild synthetic procedure.

Results and discussion

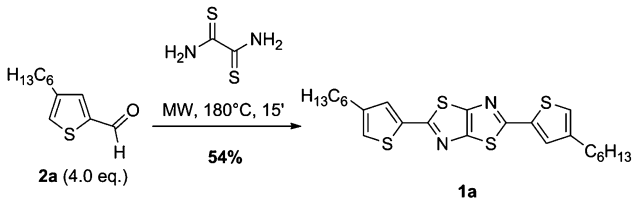
Optimization of the reaction conditions was carried out using 2-methoxybenzaldehyde **2b** as the model substrate (Table 1) to generate thiazolo[5,4-*d*]thiazole **1b**.

This substrate was chosen because it is inexpensive and readily available, and the corresponding product could be easily obtained in high purity by a simple precipitation followed by recrystallization. When a (4 : 1) mixture of aldehyde and dithiooxamide was irradiated under solventless conditions at 150 °C for 30 min, 2,5-bis(2-methoxyphenyl)-thiazolo[5,4-*d*]-thiazole **1b** was obtained in 48% yield after recrystallization (entry 1). The aldehyde/dithiooxamide 4 : 1 ratio was selected to ensure complete dissolution of dithiooxamide under solvent-free conditions. Such result was already comparable to that obtained with the classical thermal procedure by employing a much larger amount of aldehyde **2b** (47% yield, 8.0 eq.).[15] However, analysis of the ^{1}H-NMR spectrum of the crude reaction mixture revealed the presence of a byproduct, which we identified as symmetrical compound **3** (Fig 2), based on the assignment of the relevant spectral peaks (see ESI‡). Such compound is a likely intermediate in the cyclization pathway;[6] formation of a similar species was already observed in the thermal reaction of salicylaldehyde with dithiooxoamide,[15] and in that case it was shown that it could be converted to the desired product by heating at 250–270 °C, with or without addition of a mild oxidant like sulfur. Therefore, we reasoned that the yield of our reaction could be further improved by addition of an oxidant, in order to facilitate the last dehydrogenation step and achieve full aromatization to product **1b**.

Indeed, when the crude mixture was directly dissolved in THF and reacted with 0.25 eq. of DDQ (Table 1, entry 2) at reflux for 10 min the yield was improved to 61%. Use of 0.5 eq. of DDQ led to a further increase to 70% (entry 3), and employment of a cheaper, structurally related oxidant such as chloranil gave practically the same result (68%, entry 4). Importantly, when the same conditions were applied using conventional thermal heating a lower yield of the desired compound was obtained (48%, entry 5) showing that MW activation is beneficial for the reaction outcome. A reasonable yield could be still obtained when lowering the amount of aldehyde to 3.0 eq. (entry 6), while further experiments showed that variation of the temperature (entries 7 and 8) or employment of a longer reaction time were not productive in this case.

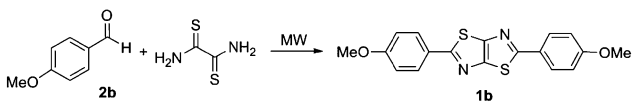
Microwave reactions under solvent-free conditions are attractive since they are usually characterized by reduced waste, low costs and simplicity in processing and handling. However, in the case of solid reaction partners or when a large excess of one reagent should be avoided, use of a solvent can be advantageous. For this reason we decided to investigate also the reaction outcome using nitrobenzene as the reaction medium, a solvent previously employed in thermal procedures.[21]

Although we found that the reaction was less efficient (entry 9), we observed that in the presence of solvent it was possible to obtain a reasonable yield of the product even using a strict stoichiometric amount of aldehyde (2.0 eq. entry 11), proving these as the best conditions to be used with valuable or solid substrates.



Scheme 1 MW-assisted synthesis of thiazolo[5,4-*d*]thiazole **1a**.

Table 1 Optimization of reaction conditions for the preparation of thiazolothiazole **1b** from 2-methoxybenzaldehyde **2b**



Entry	**2b**[a]	*T* (°C)	DDQ[a]	Yield[b]
1	4.0	150	—	48%
2	4.0	150	0.25	61%
3	4.0	150	0.50	70%
4	4.0	150	0.50[c]	68%
5[d]	4.0	150	0.50	48%
6	3.0	150	0.75	61%
7	4.0	100	0.50	—
8	4.0	180	0.75	52%
9[e]	4.0	150	0.50	59%
10[e]	3.0	150	0.50	63%
11[e]	2.0	150	0.50	55%

[a] Equivalents used in the reaction relative to dithiooxamide. [b] Yield of isolated compound. Reaction time was 30 min for all entries. [c] Chloranil was used instead of DDQ as the oxidant. [d] Reaction performed without MW activation. [e] Nitrobenzene ($C_6H_5NO_2$) was used as the solvent.

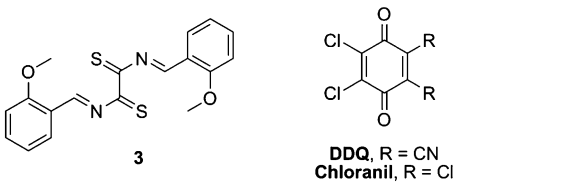


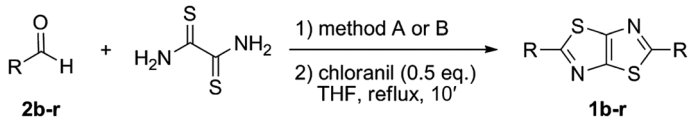
Fig. 2 Structure of intermediate **3** and of the oxidants used in this work.

Having found two sets of efficient reaction conditions, the scope of the MW-assisted procedures was assessed by reacting a range of aldehydes both under solvent-free conditions (method A) and in solution (method B). The results obtained are reported in Table 2, together with the best results previously described in the literature for known compounds.

The two methods gave in most of the cases the expected product in good yield (up to 81%) and high purity. Solvent-free conditions generally provided better results, except in the cases of products **1d,e** (entries 3, 4). The procedure was suitable both for substituted aromatic (entries 1–7) and heteroaromatic (entries 8–13) aldehydes.

With these substrates, superior yields compared to the literature were often obtained (up to 76%, entries 1, 3, 8, 9, 11). In some other cases, similar yields were obtained but a much smaller excess of aldehyde (entries 2, 4) was required. Finally, only for two substrates this methodology afforded results comparable to the literature (entries 5, 10). The best result was obtained with EDOT-aldehyde **2n**, which gave the corresponding product in 81% yield (entry 13). Unfortunately, compounds **1g** and **1h** were almost completely insoluble in a wide range of organic solvents, which hampered their full spectroscopic characterization (entries 6–7). In the case of compound **1h**, it was possible to detect the corresponding molecular peaks by direct infusion mass spectrometry, which showed the typical distribution pattern of a tetrachloro-substituted compound. On the other hand, in order to confirm indirectly the formation of **1g**, we reasoned that a more soluble compound could be obtained by introduction of long alkyl chains. Therefore, the solid obtained after crystallization was reacted with 1-octyne, under heterogeneous Pd-catalyzed Sonogashira conditions,[27] and the soluble tetraalkyl-substituted bisaryl-thiazolothiazole **4** was isolated after flash column chromatography (Scheme 2). It should be pointed out that this reaction was carried out under substantially heterogeneous conditions, and at the end four new carbon–carbon bonds were formed. Preparation of compound **4**, besides proving the actual formation of **1g**, demonstrates the synthetic utility of the present procedure when starting from halo-substituted aryl aldehydes. Indeed, thiazolothiazoles such as **1g**, being able to undergo further synthetic manipulation, constitute useful building blocks for a series of applications such as those already outlined, where compounds featuring extended π-structures are often required.[8–13]

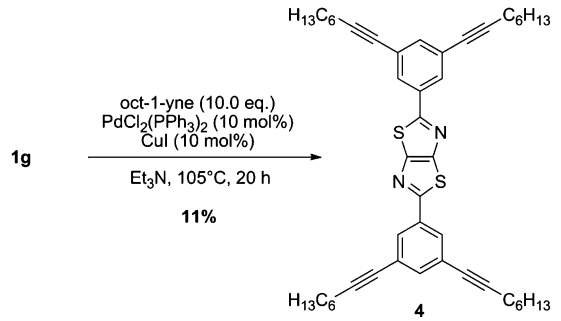
Table 2 Scope of MW activated condensation/oxidation sequence to thiazolo[5,4-*d*]thiazoles



2b-r **1b-r**

Entry	R	Product	Method[a,b]	Isolated yield	Lit. yield (eq. of 2)
1	2-CH_3O-Ph (**2b**)	**1b**	A	68%	47% (ref. 15) (8)
			B	55%	
2	Ph (**2c**)	**1c**	A	73%	78% (ref. 15) (10)
			B	66%	
3	2-Br-Ph (**2d**)	**1d**	A	35%	35% (ref. 25) (10)
			B	58%	
4	4-*t*Bu-Ph (**2e**)	**1e**	A	46%	52% (ref. 26) (3.5)
			B	47%	
5	2-OH-Ph (**2f**)	**1f**	A	46%	45% (ref. 25) (2)
			B	30%	
6	3,5-Br_2-Ph (**2g**)	**1g**	B	69%[c]	—
7	2,4-Cl_2-Ph (**2h**)	**1h**	B	72%[c]	—
8	2-Thienyl (**2i**)	**1i**	A	72%	36% (ref. 11*a*) (2)
			B	49%	
9	2-Furyl (**2j**)	**1j**	B	66%	40% (ref. 15) (13)
10	4-Pyridyl (**2k**)	**1k**	B	66%	60% (ref. 21) (2)
11	2-Pyridyl (**2l**)	**1l**	B	76%	60% (ref. 21) (2)
12	5-Thiazolyl (**2m**)	**1m**	B	75%	—
13	2-(3,4-Ethylendioxy)thienyl (**2n**)	**1n**	B	81%	—
14	*n*-Hexyl (**2o**)	**1o**	A	54%[d]	—
			B	40%[d]	
15	Cyclohexyl (**2p**)	**1p**	A	40%	—
			B	21%	
16	*tert*-Butyl (**2q**)	**1q**	B	33%	—
17	Styryl (**2r**)	**1r**	A	6%	7% (ref. 15) (9)
			B	9%	

[a] Method A: aldehyde **2** (4.0 eq.), dithioxamide (1.0 eq.), MW, 150 °C, 30′, neat. [b] Method B: aldehyde **2** (2.0 eq.), dithioxamide (1.0 eq.), nitrobenzene, MW, 150 °C, 30′. [c] Due to the almost complete insolubility in a wide range of organic solvents, full characterization was not possible. [d] Purified by flash column chromatography.



Scheme 2 Elaboration of compound **1g** by means of a Pd-catalyzed Sonogashira reaction.

Remarkably, product formation occurred also with challenging substrates such as primary, secondary and tertiary aliphatic aldehydes **2o–q**, albeit with moderate yields (33–54%, entries 14–16). Conversion of such substrates was usually unsuccessful under classic conditions, due to the formation of aldol-type byproducts (for enolizable aldehydes) and difficult final aromatization (formation of a shorter and less stabilized π-system); employment of the present methodology allowed to overcome such obstacles. Moreover, this was the first time that a synthetic procedure for the preparation of thiazolo[5,4-*d*]-thiazoles was reported to work both on aromatic and aliphatic substrates. Indeed, to date the preparation of only one aliphatic product was described.[7a,b,26] Finally, the method found a limitation in the use of α-β-unsaturated aldehydes as, when cinnamaldehyde **2r** was subjected to the reaction conditions, the corresponding product could be isolated only in low yields (entry 17).

Conclusions

In summary, we have developed a rapid and simple procedure for the synthesis of thiazolo[5,4-*d*]thiazoles through microwave activation of the condensation of dithioxoamide with aromatic aldehydes, followed by oxidation (aromatization). These useful products were obtained in good yields, using mild conditions and often reducing the excess of aldehydes employed in the process. Application of the reaction both on aromatic and aliphatic aldehydes, as well as further elaboration of the reaction products by cross-coupling chemistry, was demonstrated.

Experimental section

General remarks

All reactions were performed under an inert nitrogen atmosphere in a flame- or oven-dried apparatus. Microwave-assisted transformations were carried out using a *CEM Discover Bench-Mate* reactor at fixed temperature (surface sensor monitoring) and variable power (max. power 300 W). Liquid aldehydes were distilled under vacuum before use. 3,4-Ethylenedioxythiophene-2-carboxaldehyde[28] was prepared according to a published procedure. All other chemicals employed were commercially available and used as received. Petroleum ether was the 40–60 °C boiling fraction. Thin layer chromatography was carried out on aluminum-supported Merck 60 F254 plates; detection was carried out using UV light and permanganate or molybdophosphoric acid solutions followed by heating. Flash column chromatography was performed using Merck Kieselgel 60 (300–400 mesh) as the stationary phase. ^{1}H-NMR spectra were recorded at 300 or 400 MHz, and ^{13}C-NMR spectra were recorded at 75.5 or 100.6 MHz. Chemical shifts were referenced to the residual solvent peak ($CDCl_3$, δ 7.26 ppm for ^{1}H-NMR and δ 77.16 ppm for ^{13}C-NMR; pyridine-d_5, δ 7.22, 7.58 and 8.74 ppm for ^{1}H-NMR, δ 123.9, 135.9 and 150.4 ppm for ^{13}C-NMR; DMSO-d_6, δ 2.50 ppm for ^{1}H-NMR). FT-IR spectra were recorded in the range 4000–400 cm^{-1} with a 2 cm^{-1} resolution. ESI-MS spectra were obtained by direct injection of the sample solution and are reported in the form *m*/*z*. Melting points are uncorrected.

General procedure A

In a microwave vial equipped with a magnetic stirrer were introduced aldehyde **2** (8.0 mmol, 4.0 eq.) and dithiooxamide (2.0 mmol, 1.0 eq.). The resulting mixture was heated under microwave irradiation at 150 °C for 30 min, then allowed to cool down to room temperature. The reaction mixture was diluted with THF (*ca.* 5 mL) and transferred in a flask, then chloranil (1.0 mmol, 0.5 eq.) was added to the reaction mixture, which was heated to reflux and stirred for 10 min. After this time heating was interrupted and methanol (*ca.* 10 mL) was added to the reaction mixture, which was cooled down to 0 °C. The precipitated solid was filtered and washed with methanol, and recrystallized from THF to give pure thiazolo[5,4-*d*]thiazole **1**.

General procedure B

In a microwave vial equipped with a magnetic stirrer were placed aldehyde **2** (2.0 mmol, 2.0 eq.), dithiooxamide (1.0 mmol, 1.0 eq.) and nitrobenzene (1 mL). The resulting mixture was heated under microwave irradiation at 150 °C for 30 min, after which it was allowed to cool down to room temperature. THF (*ca.* 5 mL) and chloranil (0.5 mmol, 0.5 eq.) were added to the reaction mixture, which was transferred to a flask, heated to reflux and stirred for 10 min. After this time heating was interrupted and methanol (*ca.* 10 mL) was added to the reaction mixture, which was cooled down to 0 °C. The solid was filtered, washed with methanol and recrystallized from THF to give pure thiazolo[5,4-*d*]thiazole **1**.

2,5-Bis(2-methoxyphenyl)-thiazolo[5,4-*d*]thiazole(1b).[15] Aldehyde **2b** (1.09 g, 8.00 mmol) was reacted with dithiooxamide (240 mg, 2.00 mmol) following general procedure A. After purification, compound **1b** (482 mg, 68% yield) was obtained as a pale brown solid; mp = 260–261 °C (lit.[15] 253–254 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.45 (2H, dd, J = 7.9 and 1.7 Hz), 7.42 (2H, td, J = 7.4 and 1.7 Hz), 7.12 (2H, t, J = 8.2 Hz), 7.06 (2H, d, J = 8.3 Hz), 4.08 (6H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 163.5, 156.6, 152.1, 131.1, 128.6, 123.1, 121.4, 111.8, 55.9; IR (KBr) cm^{-1} 3078, 2832, 1582; MS (ESI) *m*/*z* 355 ($M + H^+$, 100%).

2,5-Diphenylthiazolo[5,4-*d*]thiazole (1c).[15] Aldehyde **2c** (849 mg, 8.00 mmol) was reacted with dithiooxamide (240 mg, 2.00 mmol) following general procedure A. After purification,

compound **1c** (430 mg, 73% yield) was obtained as a yellow solid; mp = 196–198 °C (lit.[15] 209–210 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.99–8.02 (4H, m), 7.47–7.50 (6H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 169.3, 151.0, 134.1, 130.8, 129.3, 126.5; IR (KBr) cm^{-1} 3059, 1570; MS (ESI) *m*/*z* 295 (M + H^+, 100%).

2,5-Bis(2-bromophenyl)-thiazolo[5,4-*d*]thiazole (1d).[25] Aldehyde **2d** (370 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1d** (262 mg, 58% yield) was obtained as a pale green solid; mp = 228–229 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.06 (2H, dd, J = 8.0 and 1.6 Hz), 7.75 (2H, dd, J = 8.0 and 1.2 Hz), 7.46 (2H, td, J = 7.6 and 1.2 Hz), 7.33 (2H, td, J = 8.0 and 1.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 166.8, 151.9, 134.5, 134.4, 132.1, 131.3, 127.9, 121.7; IR (KBr) cm^{-1} 3055, 1570, 1026; MS (ESI) *m*/*z* 453 (M + H^+, 100%), 455 (50%), 451 (50%).

2,5-Bis(4-*tert*-butylphenyl)-thiazolo[5,4-*d*]thiazole (1e).[26] Aldehyde **2e** (324 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1e** (187 mg, 47% yield) was obtained as a pale yellow solid; mp = 285–287 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.92 (4H, d, J = 8.1 Hz), 7.49 (4H, d, J = 8.4 Hz), 1.37 (18H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 169.1, 154.3, 150.7, 131.5, 126.3, 126.2, 35.1, 31.3; IR (KBr) cm^{-1} 3058, 2962, 1517; MS (ESI) *m*/*z* 407 (M + H^+, 100%).

2,5-Bis(2-hydroxyphenyl)-thiazolo[5,4-*d*]thiazole (1f).[15,21] Aldehyde **2f** (977 mg, 8.00 mmol) was reacted with dithiooxamide (240 mg, 2.00 mmol) following general procedure A. After purification, compound **1f** (300 mg, 46% yield) was obtained as a light brown solid; mp = 303–305 °C (lit.[15] 300–302 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 11.39 (2H, s), 7.65 (2H, d, J = 7.9 Hz), 7.38 (2H, t, J = 8.3 Hz), 7.10 (2H, d, J = 8.3 Hz), 6.98 (2H, t, J = 8.1 Hz); ^{13}C-NMR (75 MHz, pyridine-d_5) δ_C 166.7, 157.2, 151.3, 132.2, 128.6, 121.2, 120.4, 117.9; IR (KBr) cm^{-1} 3212, 3038, 1576; MS (ESI) *m*/*z* 327 (M + H^+, 100%).

2,5-Bis(3,5-dibromophenyl)-thiazolo[5,4-*d*]thiazole (1g). Aldehyde **2g** (528 mg, 2.01 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1g** (419 mg, 69% yield) was obtained as a pale brown solid, which was insoluble in all the organic solvents tested. IR (KBr) cm^{-1} 3074, 1580, 1038.

2,5-Bis(2,4-dichlorophenyl)-thiazolo[5,4-*d*]thiazole (1h). Aldehyde **2h** (350 mg, 2.01 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1h** (311 mg, 72% yield) was obtained as a brown solid, which was insoluble in all the organic solvents tested. IR (KBr) cm^{-1} 3071, 1582, 1065; MS (ESI) *m*/*z* 431 (75%), 433 (M + H^+, 100%), 435 (50%), 437 (11%), 439 (1%).

2,5-Bis(thiophen-2-yl)-thiazolo[5,4-*d*]thiazole (1i).[11a,29] Aldehyde **2i** (897 mg, 8.01 mmol) was reacted with dithiooxamide (240 mg, 2.00 mmol) following general procedure A. After purification, compound **1i** (441 mg, 72% yield) was obtained as a yellow solid; mp = 244–245 °C (lit.[29] 246 °C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.58 (2H, dd, J = 3.7 and 1.1 Hz), 7.47 (2H, dd, J = 5.0 and 1.1 Hz), 7.12 (2H, dd, J = 5.0 and 3.7 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 162.7, 149.9, 137.7, 128.8, 128.3, 126.9; IR (KBr) cm^{-1} 3116, 1571; MS (ESI) *m*/*z* 307 (M + H^+, 100%).

2,5-Bis(fur-2-yl)-thiazolo[5,4-*d*]thiazole (1j).[15,29] Aldehyde **2j** (192 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, 181 mg (0.66 mmol) of compound **1j** (181 mg, 66% yield) was obtained as a dark green solid; mp = >250 °C (dec.) (lit.[15] 238–240 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.56 (2H, d, J = 1.5 Hz), 7.08 (2H, d, J = 3.3 Hz), 6.59 (2H, dd, J = 3.6 and 2.1 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 158.8, 150.7, 148.8, 144.4, 112.8, 110.3; IR (KBr) cm^{-1} 3111, 1497; MS (ESI) *m*/*z* 275 (M + H^+, 100%).

2,5-Bis(pyridine-4-yl)-thiazolo[5,4-*d*]thiazole (1k).[21,30] Aldehyde **2k** (214 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1k** (196 mg, 66% yield) was obtained as a light brown solid; mp = 301–304 °C (lit.[21] 300–302 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.78 (4H, d, J = 6.6 Hz), 7.87 (4H, d, J = 6.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 167.6, 152.5, 151.0, 140.6, 120.2; IR (KBr) cm^{-1} 3038, 1596; MS (ESI) *m*/*z* 297 (M + H^+, 100%).

2,5-Bis(pyridine-2-yl)-thiazolo[5,4-*d*]thiazole (1l).[13b,21] Aldehyde **2l** (214 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1l** (225 mg, 76% yield) was obtained as a brown solid; mp = 334–335 °C (lit.[21] 325–326 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.66 (2H, d, J = 4.5 Hz), 8.24 (2H, d, J = 7.5 Hz), 7.85 (2H, td, J = 7.7 and 1.7 Hz), 7.37 (2H, dd, J = 7.5 and 4.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 171.0, 153.4, 151.6, 149.8, 137.3, 125.2, 120.1; IR (KBr) cm^{-1} 3056, 1570; MS (ESI) *m*/*z* 297 (M + H^+, 100%).

2,5-Bis(1,3-thiazol-5-yl)-thiazolo[5,4-*d*]thiazole (1m). Aldehyde **2m** (226 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1m** (231 mg, 75% yield) was obtained as a brown solid; mp = 295–297 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.91 (2H, s), 8.37 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 160.0, 155.2, 150.6, 142.5, 133.4; IR (KBr) cm^{-1} 3048, 1533; MS (ESI) *m*/*z* 309 (M + H^+, 100%). HRMS (ESI, ion trap) *m*/*z* calcd for $C_{10}H_5N_4S_4$ [M + 1]$^+$ 308.9392. Found 308.9395.

2,5-Bis(2,3-dihydrothieno[3,4-*b*][1,4]-dioxin-5-yl)-thiazolo [5,4-*d*]thiazole (1n). Aldehyde **2n** (340 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. After purification, compound **1n** (341 mg, 81% yield) was obtained as a brown solid. mp = >350 °C (dec.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H 6.94 (2H, s), 4.50–4.53 (4H, m), 4.33–4.36 (4H, m); IR (KBr) cm^{-1} 3107, 2926, 1507, 1065; MS (ESI) *m*/*z* 423 (M + H^+, 100%). HRMS (ESI, ion trap) *m*/*z* calcd for $C_{16}H_{11}O_4N_2S_4$ [M + 1]$^+$ 422.9596. Found 422.9596. Due to the low solubility of compound **1n** in most organic solvents it was not possible to record a suitable ^{13}C-NMR spectrum.

2,5-Dihexyl-thiazolo[5,4-*d*]thiazole (1o). Aldehyde **2o** (228 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) in 1.0 mL of nitrobenzene, following general procedure B. Purification by flash column chromatography (SiO_2; PE/

Et_2O = 10/1) afforded compound **1o** (124 mg, 40%yield) as a pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 3.04 (4H, t, J = 7.6 Hz), 1.82 (4H, q, J = 7.4 Hz), 1.25–1.47 (12H, m), 0.83–0.92 (6H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 172.6, 148.4, 35.1, 31.6, 29.9, 28.8, 22.6, 14.2; IR (KBr) cm^{-1} 2927, 1467; MS (ESI) m/z 311 (M + H$^+$, 100%). HRMS (ESI, ion trap) m/z calcd for $C_{16}H_{27}N_2S_2$ [M + 1]$^+$ 311.1610. Found 311.1615.

2,5-Dicyclohexyl-thiazolo[5,4-*d*]thiazole (1p). Aldehyde **2p** (897 mg, 8.01 mmol) was reacted with dithiooxamide (240 mg, 2.00 mmol) following general procedure A. After purification, compound **1p** (245 mg, 40% yield) was obtained as a light brown solid; mp = 140–141 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 3.03 (2H, tt, J = 11.4 and 3.2 Hz), 2.14–2.19 (4H, m), 1.84–1.89 (4H, m), 1.72–1.77 (2H, m), 1.52–1.66 (4H, m), 1.26–1.47 (6H, m); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 178.0, 148.0, 44.1, 33.6, 26.1, 25.9; IR (KBr) cm^{-1} 2923, 1465; MS (ESI) m/z 307 (M + H$^+$, 100%); anal. calcd for $C_{16}H_{22}N_2S_2$: C, 62.70; H, 7.24; N, 9.14. Found: C, 62.94; H, 7.59; N, 9.13%.

2,5-Di-*t*-butyl-thiazolo[5,4-*d*]thiazole (1q). Aldehyde **2q** (172 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) and 1.0 mL of nitrobenzene, following general procedure B. Purification by flash chromatography (SiO_2; PE/Et_2O = 10/1) afforded compound **1q** (84 mg, 33% yield) as a brown solid; mp = 109–111 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 1.48 (18H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 182.4, 148.4, 39.0, 30.7; IR (KBr) cm^{-1} 2961, 1484; MS (ESI) m/z 255 (M + H$^+$, 100%). Anal. calcd for $C_{12}H_{18}N_2S_2$: C, 56.65; H, 7.13; N, 11.01. Found: C, 56.33; H, 7.01; N, 10.64%.

2,5-Distyryl-thiazolo[5,4-*d*]thiazole (1r).[15] Aldehyde **2r** (264 mg, 2.00 mmol) was reacted with dithiooxamide (120 mg, 1.00 mmol) and 1.0 mL of nitrobenzene, following general procedure B. Compound **1r** (31 mg, 9% yield) was obtained as a black solid; mp = >260 °C (lit.[15] 242–243 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.55–7.58 (4H, m), 7.49 (2H, d, J = 16.2 Hz), 7.35–7.44 (6H, m), 7.30 (2H, d, J = 16.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 168.3, 150.5, 135.5, 135.1, 129.5, 129.1, 127.4, 122.2; IR (KBr) cm^{-1} 3057, 1653, 1570; MS (ESI) m/z 347 (M + H$^+$, 100%).

2,5-Bis[3,5-di(oct-1-yn-1-yl)phenyl]-thiazolo[5,4-*d*]thiazole (4). Compound **1g** (110 mg, 0.18 mmol), was suspended into triethylamine (6.0 mL), and reacted with oct-1-yne (199 mg, 1.80 mmol), CuI (3.4 mg, 0.018 mmol), and $Pd(PPh_3)_2Cl_2$ (13 mg, 0.018 mmol). The resulting slurry was heated to 105 °C and stirred for 20 h, then it was cooled to room temperature. The reaction mixture was filtered on a short pad of Celite® and the filter cake washed several times with $CHCl_3$; the filtrate solution was washed with water (100 mL) and brine (100 mL) and dried with Na_2SO_4. Evaporation gave a dark oil which was purified by flash column chromatography (SiO_2, PE/Et_2O = 98/2) to give, after further recrystallization from AcOEt, pure compound **4** (15 mg, 11% yield) as a yellow sticky solid; ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.90 (4H, d, J = 1.4 Hz), 7.48 (2H, s), 2.42 (8H, t, J = 7.1 Hz), 1.55–1.65 (8H, m), 1.46–1.49 (8H, m), 1.31–1.36 (16H, m), 0.92 (12H, t, J = 6.9 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 168.2, 151.2, 136.5, 134.1, 128.4, 125.5, 92.4, 79.3, 31.5, 28.8, 28.7, 22.7, 19.6, 14.3; IR (KBr) cm^{-1} 2929, 2229, 1582, 1466; MS (ESI) m/z 727 (M + H$^+$, 100%). HRMS (ESI, ion trap) m/z calcd for $C_{48}H_{59}N_2S_2$ [M + 1]$^+$ 727.4114. Found 727.4113.

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