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# Direct Access to Thieno[3,4-b]thiophenes via Elemental Sulfur-Promoted Sulfurative Tetramerization of Acetophenones

 Thanh Binh Nguyen<sup>\*a</sup> and Pascal Retailleau

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**Thieno[3,4-b]thiophene core could be conveniently obtained via one-pot sulfurative tetramerization of acetophenones using a ternary system comprised of elemental sulfur, base and DMSO under simple heating conditions. The structure of the products was verified by X-ray crystallography.**

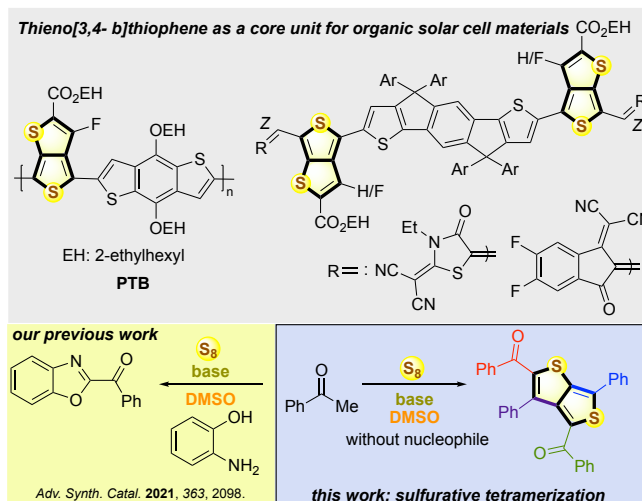
The thiophene moiety is one of the most widespread organosulfur heterocycles present in numerous biologically active molecules<sup>1</sup> as well as functional materials.<sup>2</sup> Recently, thiophene-containing functional materials have played a central role in the development of organic optoelectronics. Compared to benzene derivatives, thiophene analogs with less steric requirement display lower aromaticity and could provide extra sulfur-sulfur interactions, especially in the solid state.<sup>3</sup>

Among various thiophene scaffolds, thieno[3,4-b]thiophene with two non-symmetrically fused thiophene ring with four functionalizable position, has emerged as an excellent scaffold for the development of optoelectronic materials in both small-molecule and polymeric versions (Scheme 1). These molecules were studied for the development of high-performance optoelectronic devices such as organic photovoltaics (OPVs), organic field effect transistors (OFETs), and organic light-emitting diodes (OLEDs).<sup>3</sup>

The available methods leading to thieno[3,4-b]thiophene consist of numerous steps and they rely on stepwise assembly of their building blocks starting from functionalized monothiophene substrates, involving transition metal catalysts as well as various sulfurating agent for the formation of second thiophene ring.

During the course of our exploration of new organic reactions involving elemental sulfur,<sup>4</sup> we have been interested in the development of oligomerization as a mean of building complex structures from simple, inexpensive and readily available

organic. In a single operation under simple reaction conditions involving sulfur, organic substrates such as benzylamines,<sup>5</sup> acetophenones,<sup>6</sup> chalcones,<sup>7</sup> phenylacetonitriles<sup>8</sup> and phenylacetic acids<sup>9</sup> have been found to undergo di-, tri-, and hexamerization. As part of an exploration of the reactivity of acetophenones with various organic substrates, we have investigated their oxidative condensation with a variety of nitrogen nucleophiles in the presence of sulfur, acting as oxidant, catalyst and/or sulfur source.<sup>10</sup> For example, in the presence of *o*-aminophenols as nucleophiles, 2-benzoylbenzoxazoles were formed (Scheme 1). From a mechanistic viewpoint, the condensed heterocyclic products might be considered involving sulfurated intermediate of the methyl group of acetophenones.



Scheme 1. Thieno[3,4-b]thiophene Unit in Solar Cell Materials and Direct Synthesis from S<sub>8</sub> and Acetophenones

In the absence of nucleophiles, we questioned if such intermediate could be react with other acetophenone molecules, leading to sulfur-containing oligomer molecules. Accordingly, we have reacted acetophenone **1a** with 2 equiv of

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sulfur in dimethyl sulfoxide (DMSO, 1.5 equiv) using DABCO (0.5 equiv) as a sulfur activator in the absence of other nitrogen nucleophiles. To our surprise, upon heating at 80 °C for 16 h (Table 1, entry 1), a tetrameric product **2a** was formed, which was easily isolated as a bright yellow solid by washing the crude reaction mixture with methanol followed by heating in vacuo (0.01 mmHg) at 80–100 °C to remove volatiles, including unreacted sulfur.

In its pure state, this compound as well as its derivatives (*vide infra*) were found to be very soluble in chloroform. The molecules displayed a characteristic <sup>1</sup>H spectra with four sets of phenyl signals. Interestingly, compound **2a** crystallized in the monoclinic space group *P2<sub>1</sub>/c*, its molecular structure was readily determined by X-ray diffraction as depicted in Figure 1: a thieno[3,4-*b*]thiophene core which turned out to be tetrasubstituted by two benzoyl and two phenyl groups. Phenyl rings in C-2 and C-6 carbonyl positions are almost parallel to each other (dihedral angle of 16.4°) and the intramolecular centroid-centroid distance is 3.54 Å. The distance becomes much longer (4.51 Å) between those in C-2 and C-1 carbonyl positions on the same side of the thieno[3,4-*b*]thiophene. The carbonyl group oriented in anti-parallel fashion regarding that in position C-1, rotates the benzoyl groups away for their two other partners (respective dihedral angles above 58°). On the other side, the phenyl on position C-5 is less twisted (31.0°) out of the mean plane made by the thieno[3,4-*b*]thiophene core than the other phenyl groups in positions C-1 carbonyl, C-2, and C-6 carbonyl (respective dihedral angles of 72.3°, 50.1° and 50.6°).

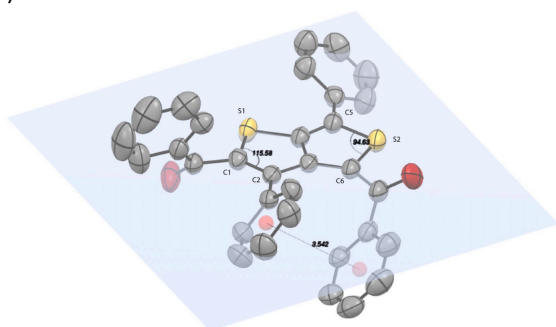


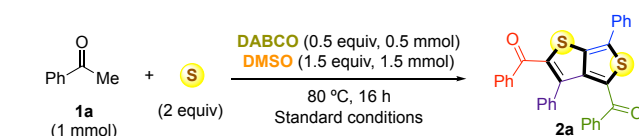
Figure 1. Ortep view of **2a** (CCDC 2194328). The thieno[3,4-*b*]thiophene mean plane is underscored by the light blue quadrilateral. Only two angle values are reported as unusual when compared with structures deposited with the Cambridge Crystallographic Database accessed via *Mogul* (Bruno *et al.*, 2004) [*Z*-score] = 2.22 and 2.14 for C6 S2 C5 vs 91.1° (mean value for 122 hits) and C2 C1 S1 vs 112.2° (mean value for 100 hits) respectively. All other bond distances, angles, and torsion angles fall within the normal ranges. Red spheres indicate centroids of phenyl groups with intramolecular  $\pi$ - $\pi$  stacking interactions.

Structurally, although only two sulfur atoms are required to form the tetramer **2a**, the reaction is best performed with two equivalent of atomic sulfur. Lowering the sulfur content to one equiv decreased significantly the efficiency of the formation of tetramer **2a** and resulted in a nearly equimolar of unchanged acetophenone and benzoyldithioformic salt of DABCO, as confirmed by <sup>1</sup>H NMR of the crude mixture (entry 2). On the other hand, increasing the sulfur content more than two equiv did not lead to any appreciable improvement of the yield of

tetramer (entry 3). The reaction could be accelerated significantly at higher temperatures (entries 4–5) and led to high yield of **2a** at 120 °C. The base loading played also an important role. With 20 mol % base, benzoyldithioformic salt of DABCO was formed and had detrimental effect on the yield of **2a** (entry 7). With 1 equiv of DABCO, **2a** was obtained in moderate yield via trituration with methanol from the crude reaction mixture, possibly due to higher solubility of **2a** in this case (entry 8).

While *N*-methylpiperidine was shown to be efficient to promote tetramerization (entry 9), other organic weaker bases such as *N*-methylmorpholine and pyridine (entries 10–11) as well as inorganic bases (entries 12–14) that were frequently used in the related reactions involving elemental sulfur failed to promote the reaction. Indeed, in all these cases, acetophenone **1a** remained practically intact in these cases. We emphasized that in the absence of DABCO, acetophenone reacted only slowly with sulfur in DMSO, even at 150 °C, to provide mixtures containing mainly unreactive acetophenone and other benzoyl derivatives (benzoate, benzoyldithioformate...) (entry 15). The singular and extraordinary role of DMSO in this transformation was ascertained by the fact that acetophenone **1a** remained unchanged if DMSO was replaced by other polar aprotic solvent such as *N*-methylpiperidone (entry 16), DMF or *N,N*-dimethylacetamide. Although DMSO could act as an addition oxidant, the yields dropped significantly when the reaction mixture was diluted with DMSO.

Table 1. Screening of the Reaction Conditions for **1a**



Entry	Variation from the standard conditions <sup>a</sup>	yield (%) <sup>b</sup>
1	Standard conditions: <b>1a</b> (1 mmol), S (2 equiv), DABCO (0.5 equiv), DMSO (1.5 equiv), 80 °C, 16 h	72
2	S (1 equiv)	0 <sup>c,d</sup>
3	S (3 equiv)	65
4	100 °C, 6 h	56
5	120 °C, 3 h	71
6	60 °C, 16 h	0 <sup>c</sup>
7	DABCO (0.2 equiv)	34
8	DABCO (1 equiv)	51
9	<i>N</i> -Methylpiperidine (1 equiv) instead of DABCO	42 <sup>e</sup>
10	<i>N</i> -Methylmorpholine (1 equiv) instead of DABCO	0 <sup>c</sup>
11	pyridine (1 equiv) instead of DABCO	0 <sup>c</sup>
12	KF (0.5 equiv) instead of DABCO	0 <sup>c</sup>
13	Na <sub>2</sub> S•5H <sub>2</sub> O (0.5 equiv) instead of DABCO	0 <sup>c</sup>
14	Cs <sub>2</sub> CO <sub>3</sub> (0.5 equiv) instead of DABCO	0 <sup>c</sup>
15	Without DABCO, 80–150 °C	0 <sup>c</sup>
16	<i>N</i> -Methylpyrrolidone (0.1 mL) instead of DMSO	0 <sup>c</sup>

<sup>a</sup> Standard conditions: acetophenone (1 mmol), sulfur (2 mmol, 64 mg), DABCO (0.5 mmol, 56 mg), DMSO (1.5 mmol, 0.1 mL), 80 °C, 16 h. <sup>b</sup> Isolated yield by filtration unless otherwise noted. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>d</sup> Crude mixture containing starting material **1a** + benzoyldithioformate. <sup>e</sup> Purified by column chromatography.

Table 2. Sulfurative Tetramerization of Acetophenones 1

<sup>a</sup> Reaction conditions: acetophenone **1** (1 mmol), sulfur (2 mmol, 64 mg), DABCO (0.5 mmol, 56 mg), DMSO (1.5 mmol, 0.1 mL), 80 °C, 16 h. <sup>b</sup> Isolated yield by filtration. <sup>c</sup> 120 °C, 3 h.



We noticed that while **2a** is readily isolable from many crude reaction mixtures by precipitation with methanol, application of this technique to other derivatives was unsuccessful due to their higher solubility, especially in the crude mixtures. They were however be readily obtained by chromatography on silica gel.



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Acetophenones substituted by an *o*-substitution such as *o*-methyl, *o*-methoxy reacted also to give the expected tetramers. However, the purification by column chromatography or recrystallization was difficult and we were unable to obtain the desired product with acceptable purity.

Based on the result of the above experiments, we depicted in Scheme 2 a plausible reaction mechanism of the tetramerization of acetophenone **1**. Our previous observation<sup>9,11</sup> on the generation of highly reactive thiocarbonyl intermediate via oxidative sulfuration of an active methylene moiety using the ternary system comprised of elemental sulfur, base and DMSO reaction provides very useful information for establishing a reasonable mechanism of the formation of the unusual product **2**. In the present case, this ternary system transformed acetophenone **1** into thioaldehyde **C** via  $\alpha$ -mercaptan acetophenone **A**. The involvement of **C** was confirmed by the isolation of its sulfurized derivative **4c** (CCDC 2195876) from the reaction mixture of acetophenone **1c** performed at 80 °C.

Subsequent condensation of **C** with another acetophenone **1** would provide 1,2-dibenzoyl ethylene **E** via a sequence of addition-elimination. Strongly activated by two benzoyl groups, the ethylene moiety of **E** became a good Michael acceptor for addition of another acetophenone. The resulting adduct **F** underwent a cascade of sulfuration-cyclization-dehydration-aromatization to yield the key intermediate **3**. It should be noted that the last operation of oxidative aromatization to thiophene could be performed with S<sub>8</sub> or DMSO as the terminal oxidant. The incorporation of the last acetophenone unit to **3** was effected via a series of domino reactions including

condensation with acetophenone (**3**  $\rightarrow$  **I**),  $\alpha$ -sulfuration of the adduct **J**  $\rightarrow$  **K** and intramolecular electrophilic sulfuration of the first thiophene ring of **K**  $\rightarrow$  **M** with subsequent eliminative aromatization to yield **2**. The atom balance of the whole process indicates that each molecule of thieno[3,4-*b*]thiophene **2** formed as a result of the combination of four acetophenone molecules, two sulfur atoms and four oxygen atoms (or equivalent) to remove six water molecules with seven new bonds created.

In conclusion, this work provided a simple and straightforward approach for generating thieno[3,4-*b*]thiophene **2** from acetophenone **1** in the presence of the ternary system of elemental sulfur, base and DMSO. In a single operation, four acetophenone units combined with two sulfur atoms. Further studies of the physical properties of these molecules and exploitation of this new chemical transformation in synthesizing related scaffolds are currently underway.

## Conflicts of interest

There are no conflicts to declare.

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