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Facile one-pot synthesis of 2,3-thienoimides via formal [3+2] annulation reaction of 1,4-dithiane-2,5-diol and *N*-substituted imides

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ABSTRACT

A formal [3+2] annulation reaction of 1,4-dithiane-2,5-diol and *N*-substituted imides through one-pot metal-free strategy has been developed. This method could furnish 2,3-thienoimides in good to high yields.

Thiophenes have received much attention in the last few decades due to their wide applications in pharmaceuticals and material science.[1–10] Substituted thiophenes have exhibited a wide spectrum of biological activities, ranging from antianxiety,[11] antibacterial,[12,13] antiprotozoal,[14] antivirus,[15] antiproliferative,[16] LIMK1 inhibitors,[17] DPP-IV inhibitors,[18] antioxidant,[19] and insecticidal herbicide.[20–23] Moreover, polymeric thiophenes are also broadly utilized as thin-film transistors,[24,25] organic light-emitting transistors (OLET),[26] organic field-effect transistors,[27–29] chemical sensors,[30,31] and solar cells.[32,33] As outlined in Figure 1, DTS(TTPD)$_2$ was identified to be an highly efficient electron donor in solar cells.[34] T4DIM had been recognized as organic thin film transistors (OTFT) and organic light emitting transistors (OLET).[35] DTTDI exhibited a potency to become latent n-channel organic semiconductors.[36]

Despite these significant progresses in applications, to our knowledge, very few reliable and effective approaches to access this important class of 2,3-thienoimides (structure highlighted in Fig. 1) have been reported yet. Briefly, literature reported methods for the synthesis of the core structure thieno[3,4-*c*]pyrrole-4,6-dione mainly relied on the reaction of thieno[2,3-*c*]furan-4,6-dione with primary amines in thionyl chloride.[34,35,37] However, the preparation of thieno[2,3-*c*]furan-4,6-dione in itself was a time-consuming process.[38,39] On the other hand, 1,4-dithiane-2,5-diol has also been found to be an attractive synthon for the assembly of tetrahydrothiophene or thiophene derivatives.[40–44] As part of our continued interest in the development of organocatalytic method for the construction of aromatic heterocyles,[45] we described herein a formal [3+2] annulation reaction between 1,4-dithiane-2,5-diol and *N*-substituted imide, which provided a new

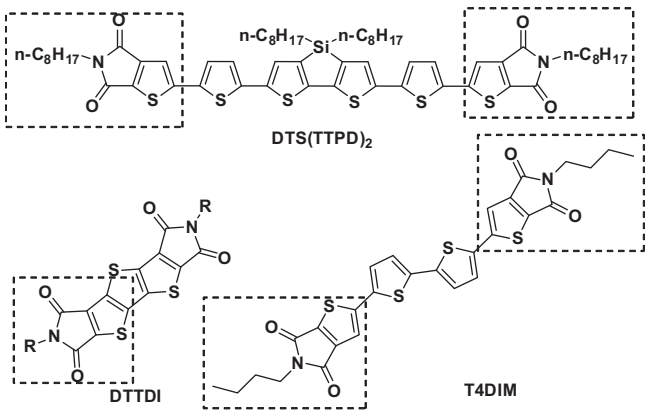

Figure 1. Typical examples of oligomeric and polymeric thiophenes.

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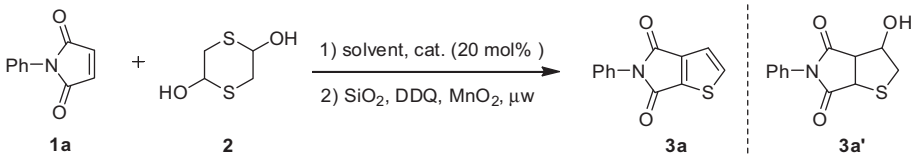
Table 1
Optimization of reaction conditions[a]



Entry	Cat.	Solvent	*T* (h)	Yield of **3a**[b] (%)
1	TEA	CH_2Cl_2	0.5	85
2	TEA	$CHCl_3$	0.5	84
3	TEA	$Cl(CH_2)_2Cl$	0.5	80
4	TEA	THF	0.5	81
5	TEA	CH_3CN	2	75
6	TEA	Benzene	8	40
7	TEA	Toluene	8	32
8	TEA	Et_2O	8	37
9	DIPEA	CH_2Cl_2	0.5	86
10	Pyridine	CH_2Cl_2	1	80
11	DEA	CH_2Cl_2	1	70
12	NaOAc	CH_2Cl_2	2	74
13	$NaHCO_3$	CH_2Cl_2	2	55
14	K_2HPO_4	CH_2Cl_2	2	72
15	NaOH	CH_2Cl_2	2	37
16	—[c]	CH_2Cl_2	2	0

[a] Reaction conditions: a mixture of **1a** (0.40 mmol), **2** (0.24 mmol), cat. (0.08 mmol) in solvent (1 mL) was stirred at room temperature for a certain period of time. The solvent was then removed and obtained solid was ground with silica gel (20 equiv, w/w), DDQ (3.0 equiv), and MnO_2 (6.0 equiv) in a mortar followed by irradiation in a laboratory microwave for 15 min.
[b] Yield of isolated product.
[c] No catalyst.

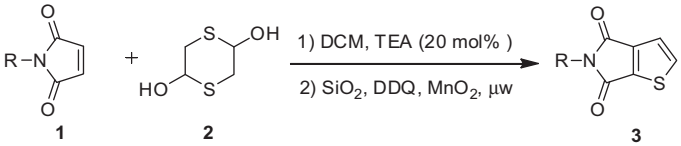
and efficient route to generate 2,3-thienoimides followed by a subsequent dehydration and aromatization sequence.

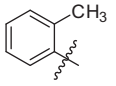
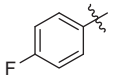
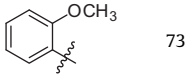
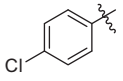
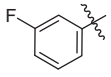
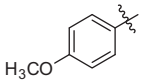
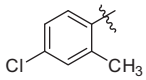
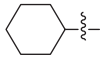
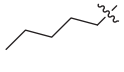
We began with an initial experiment of 1-phenyl-1*H*-pyrrole-2,5-dione **1a** and 1,4-dithiane-2,5-diol **2** catalyzed by trimethylamine (TEA). The reaction was proceeded smoothly to form an intermediate 3-hydroxyl-tetrahydrothienoimide **3a′** in DCM at room temperature. Build upon intermediate **3a′**, we then attempted to covert **3a′** into the desired 2,3-thienoimide **3a**. In terms of the structure of **3a′**, we proposed a subsequent dehydration and oxidation cascade reaction. Several oxidants (e.g., MnO_2, sulfuric acid, Oxones, DDQ) were tested independently, but all gave poor conversion (<10%). For example, the reaction mixture was directly treated with trifluoroacetic anhydride and DDQ heating at reflux for 2 days, but no desired product 2,3-thienoimide **3a** was observed. In view of high temperature might be good for dehydration and oxidation reaction, we replaced the dichloromethane with a high boiling solvent acetic acid and refluxed the reaction at 120 °C for 5 h. However, the isolated yield of **3a** was only 30%. Finally, a combination silica gel/DDQ/MnO_2/Microwave was found to be the most efficient toll to promote this reaction and afforded the desired product **3a** in 85% yield (Table 1, entry 1, 0.5 h).

To examine the generality of substrate scope, a wide range of *N*-substituted imides **1** were investigated. As described in Table 2, all reactions proceeded smoothly, providing the corresponding 2,3-thienoimides **3** in good yields. The electronic nature and the position of the substituents on the aryl ring of *N*-substituted imides had no obvious influence on the formation of the desired product **3**. Electron-withdrawing (**3b**–**c**, **3e**–**g**, and **3j**), -donating (**3d**, **3i**, and **3h**), and -neutral (**3a**, **3l**) substituents all gave good to high chemical yields. It was also noteworthy that *N*-aliphatic substituted imides were well tolerated and afforded the corresponding products in good yields (**3m** and **3n**).

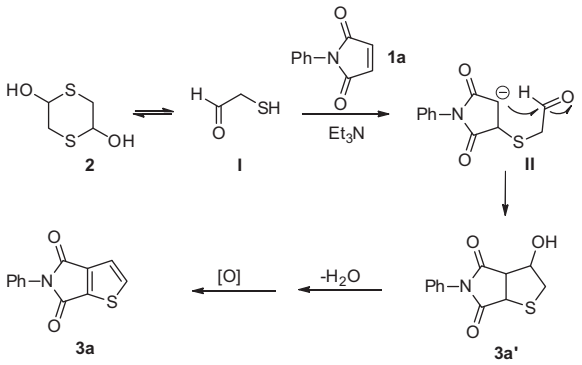
Our postulated reaction mechanism is illustrated in Scheme 1. 1,4-Dithiane-2,5-diol **2** yields intermediate mercaptoacetaldehyde

Table 2
Substrate scope



Product	R	Yield[a] (%)	Product	R	Yield[a] (%)
3a		85	**3h**		78
3b		82	**3i**		73
3c		80	**3j**		78
3d		76	**3k**		75
3e		75	**3l**		70
3f		80	**3m**		78
3g		78	**3n**		67

[a] Isolated yield after column chromatography.



Scheme 1. Proposed mechanism.

I triggered by TEA. Mercaptoacetaldehyde **I** then attacks *N*-phenyl imide **2a** to afford intermediate **II**. A subsequent intramolecular aldol reaction of intermediate **II** affords **3a**′. Lastly, a cascade of dehydration and oxidation of **3a**′ generates the desired product **3a**.

In summary, a rapid and efficient metal-free one-pot strategy has been developed. The reaction can efficiently afford 3-thienoimides in good to high yields. Considering the ready availability of the starting materials and the operational simplicity, we believe that this method will have a broad use. Further mechanistic and applications of this reaction are ongoing in our group, and more results will be reported in due course.

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Supplementary data

Supplementary data (experimental procedures and compound characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.04.097.

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