$TiCl_4$-Mediated Preparation of Thiophthalide Derivatives *via* Formal Thio-Passerini Reactions

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ABSTRACT: By the formal extension of the Passerini reaction to thiocarbonyl derivatives, the straightforward preparation of thiophtalides is disclosed. This method involves the intermediate formation of a sulfanyl-phthalide and a titanium tetrachloride-mediated isocyanide insertion reaction. When *t*-butyl thiol is used, thanks to the deprotection of the *t*-butyl group, a thiophthalide resulting from a 1,5-Mumm rearrangement is isolated. Owing to the multi-faceted activity of $TiCl_4$, all steps may conveniently be performed in one pot, starting directly from 2-formylbenzoic acids, *t*-butyl thiol and various isocyanides.

Through the years, sulfur-based skeletons have been identified as leading constituents of numerous pharmaceuticals, partly due to the fact that sulfur-lone pair interactions may serve as key conformational control elements.[1,2] Noticeably, compared to their oxygen and nitrogen analogues, the 1,3-dihydro-benzo[*c*]thiophene derivatives as well as their 1-keto analogs, thiophthalides, represent a relatively ignored class of sulfur-containing heterocycles in medicinal chemistry. Yet, talsupram (Lu 5-003), one the most studied member of this family, has been identified as a very potent norepinephrine reuptake inhibitor, while other 1,3-dihydro-benzo[*c*]thiophenes have similarly showed interesting psychotropic activities (Figure 1).[3-6] Thiophthalides, on the other hand, are equally stimulating targets considering that some of them display antithrombotic, anticonvulsant and analgesic properties.[7,8]

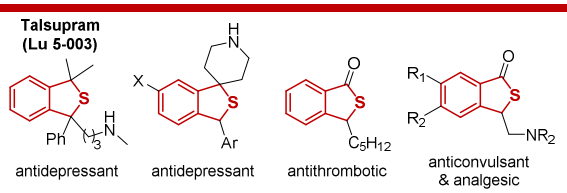
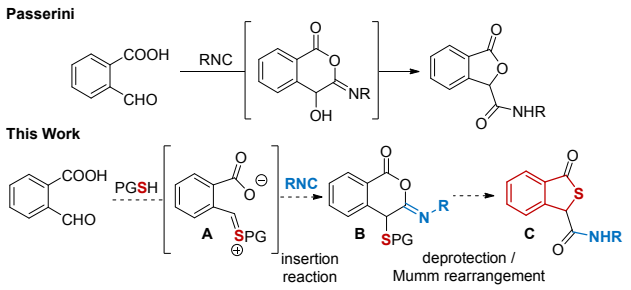


Figure 1: 1,3-Dihydro-benzo[*c*]thiophene and thiophtalide containing biologically-relevant molecules.

Whereas these compounds are typically synthesized through multistep processes or by nucleophilic additions onto thiophthalic anhydride,[3,4,7,9] the restricted available methods for their preparation have most likely hampered their use in medicinal chemistry. Accordingly, in order to allow a more thorough evaluation of the pharmacological potential of this so far overlooked chemical space, the development of new synthetic methods is highly desirable.

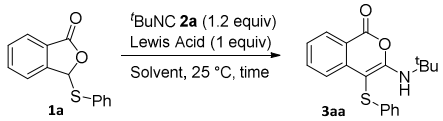
In this context, as part of our continuing interest in isocyanide based multicomponent reactions,[10] we decided to study the straightforward access to 1,3-dihydro-benzo[*c*]thiophenone (thiophthalide) derivatives by the mean of an unprecedented formal thio-Passerini reaction (Scheme 1).[11,12] Whereas the formation of phthalides from isocyanides and 2-formyl benzoic acid was originally described by Passerini,[13] the development of a thio-variant of this transformation has, to the best of our knowledge, never been reported. Actually, the achievement of this goal was definitely not trivial considering the lack of any reliable access to stable thioaldehydes.[14] For this reason, we designed an original strategy in which, starting from 2-formyl benzoic acid and the appropriate thiol partner, the *in situ* generation of a thiocarbenium species **A** would allow the required isocyanide insertion reaction (Scheme 1). Based on this hypothesis and by the careful selection of the *S*-protecting group, we anticipated that the formation of the targeted thiophthalide **C** could be achieved *via* a Mumm 1,5-acyl transfer triggered by the *in situ* *S*-deprotection of intermediate **B** (Scheme 1).

Scheme 1: Our strategy for the construction of thiophthaliddes *via* a thio-Passerini type coupling.



With this plan in mind, we initially surveyed the practicability of the insertion reaction of isocyanides into an *in situ* generated thiocarbenium **A**.[15,16] For this purpose, 3-phenylsulfanyl-phthalide **1a**[17] was prepared and submitted to a stoichiometric amount of a variety of Lewis acid in the presence of a slight excess (1.2 equiv) of *tert*-butylisocyanide **2a** in dichloromethane at room temperature (Table 1). Among the various Lewis acids tested,[18] only two allowed to obtain the desired insertion product, in the form of the tautomeric thio-isochromenone **3aa** (Table 1, entries 5 and 7). As observed by Chatani and co-workers in the specific context of the isocyanide insertion into symmetrical thioketals, best yields were achieved using titanium tetrachloride (Table 1, entry 7) but, in opposition to their study, $GaCl_3$ gave no insertion product (Table 1, entry 2).[16] Whereas other solvents were tested (Table 1, entries 8-13), none provided superior results compared to that obtained with dichloromethane, in which the use of $TiCl_4$ led to the formation of **3aa** in good 76% isolated yield (Table 1, entry 7). All attempts to perform the reaction with catalytic amounts of Lewis acids failed to give better yields.[18]

Table 1: Optimization studies of the isocyanide insertion into thiophthalides

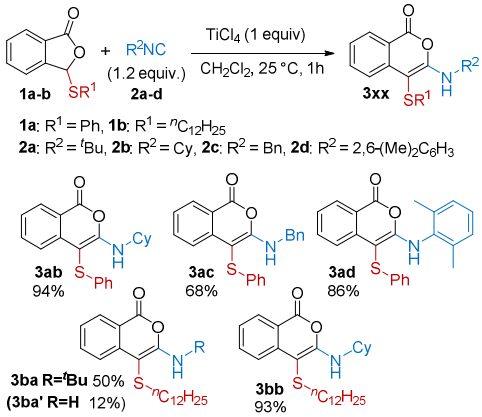


Entry	Solvent	Lewis Acid	Time (h)	Yield (%)[a]
1	CH_2Cl_2	$BF_3.OEt_2$	2	0
2	CH_2Cl_2	$GaCl_3$	2	0
3	CH_2Cl_2	$In(OTf)_3$	2	0
4	CH_2Cl_2	$Zn(OTf)_2$	2	0
5	CH_2Cl_2	$AlCl_3$	2	13
6	CH_2Cl_2	$TiCl(O\textit{i}\text{-}Pr)_3$	2	0
7	CH_2Cl_2	$TiCl_4$	1	76
8	$CHCl_3$	$TiCl_4$	1	16
9	1,2-DCE[b]	$TiCl_4$	1	41
10	Et_2O	$TiCl_4$	1	18
11	THF	$TiCl_4$	1	0
12	CH_3CN	$TiCl_4$	1	0
13	Toluene	$TiCl_4$	1	39

[a] Isolated yield. [b] DCE: 1,2-dichloroethane.

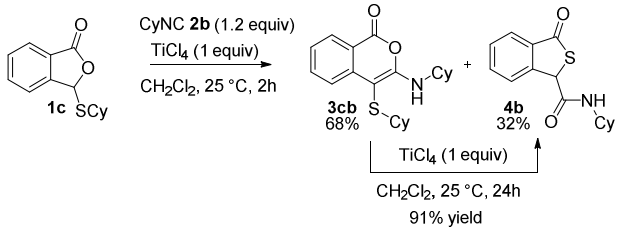
With this optimized reaction conditions in hands, sulfanylphthalides **1a** and **1b** were reacted with a set of several isocyanides (Scheme 2). Remarkably, the 3-amino-4-thio-isochromen-1-ones **3** were consistently obtained in good to excellent yields and thereby demonstrated the efficiency of this original isocyanide insertion process. While the reaction of 3-phenylsulfanyl-phthalide **1a** well tolerated the use of either aliphatic or aromatic isocyanides **2b-d**, we were satisfied to witness that the desired isocyanide insertion process could straightforwardly be extended to the *S*-alkyl substituted phthalide **1b**. Notably, the reaction between **1b** and *tert*-butylisocyanide **2a** afforded the isochromenone **3ba** in lower 50% yield, as a result of the competitive cleavage of the *tert*-butyl group leading to the corresponding free-amino compound **3ba′** (12% yield).

Scheme 2: Scope of the $TiCl_4$-promoted isocyanide insertion into thiophthalides 1a-b.



On the other hand, we were quite pleased to observe that the *S*-cyclohexyl phthalide **1c**, in reaction with **2b**, conducted to an approximately 2 to 1 mixture of the isochromenone **3cb** and the ultimately targeted thiophthalide **4b** (Scheme 3). This result seemed to confirm that the involvement of a subsequent *S*-deprotection/Mumm rearrangement sequence was an attainable task,[19,20] and somehow endorsed our thio-Passerini approach to thiophthalides. Interestingly, we could also demonstrate that $TiCl_4$ is a suitable promoter of this subsequent process. Indeed, the high yielding formation of **4b** from **3cb** could be achieved using one equivalent of this Lewis acid in dichloromethane at room temperature over a 24-hour period (Scheme 3).

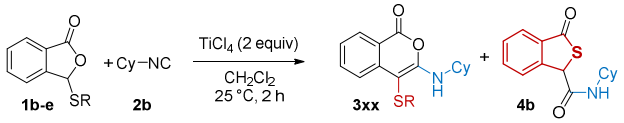
Scheme 3: Conversion of phthalide 1c into thiophathalide 4b *via* the intermediary formation of isochromenone 3cb



To optimize this thio-Passerini like process and to capitalize on the ability of $TiCl_4$ to both promote the isocyanide insertion step and the subsequent rearrangement of isochromen-1-ones, various *S*-protecting groups were then evaluated for the direct preparation of thiophthalide **4b**. For this purpose, sulfanylphthalides **1b-d** and cyclohexylisocyanide **2b** were submitted to two equivalents of $TiCl_4$ in dichloromethane at room tempera-

ture (Table 2). After two hours, the reaction was consistently quenched and, after purification, the yield of thiophthalide **4b** and that of the corresponding isochromenone were determined. As we could expect, the overall efficiency of this transformation was highly dependent of the capacity of the *S*-protecting group to stabilize the positive charge resulting from the carbon-sulfur bond rupture event. While phthalide **1b**, which possesses a linear alkyl chain, failed to give **4b**, its cyclohexyl-substituted counterpart **1c** only partially afforded 31% of the targeted thiophthalide. Conversely, the *p*-methoxybenzyl-, the benzyl- or the *t*-butyl-substituted phthalides **1d, 1e** and **1f** led straightforwardly to **4b** in 65%, 82% and 76% yield respectively.[21] However, due to an incomplete conversion in the case of the benzyl mercaptan **1e**, **1f** was selected for the rest of our studies.

Table 2: Optimization of the *S*-protecting group allowing the direct synthesis of thiophthalides from phthalides.

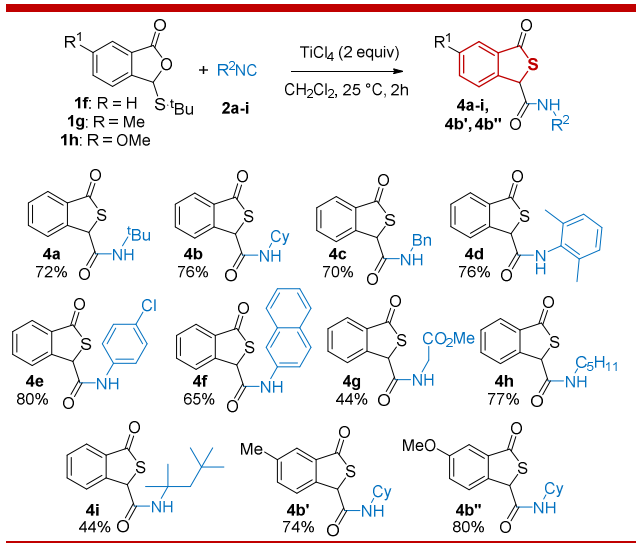


Entry	Substrate, R	**3xx**, yield	**4b** (yield)
1	**1b**, $^{n}C_{12}H_{25}$	**3bb**, 93%	-
2	**1c**, Cy	**3cb**, 69%	31%
3	**1d**, PMB[a]	**3db**, 0%	65%
4	**1e**, Bn	**3eb**, 10%	82%
5	**1f**, ^{t}Bu	**3fb**, 0%	76%

[a] PMB = *p*-methoxybenzyl.

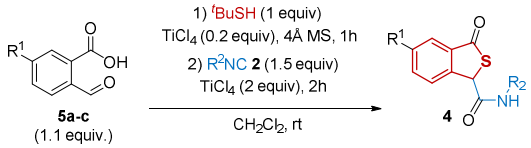
Pleasingly, this direct preparation of thiophthalides **4** from the *S*-(*t*-butyl)-substituted phthalide **1f** could be efficaciously be extended to the use of a wide range of isocyanides **2a-i** (Scheme 4). Indeed, independently of the aliphatic or aromatic nature of the isocyanide partner, the expected thiophthalides were reliably obtained with satisfactory yields. Of note, this method was also amenable to the functionalization of the aromatic moiety of the starting phthalides, considering that **1g** and **1h** similarly afforded the desired thiophthalides **4b′** and **4b″** in good 74% and 80% yield respectively.

Scheme 4: Scope of this formal thio-Passerini thiophthalide synthesis.



To push forward the boundaries of this formal thio-Passerini process, we envisioned the development of an even more straightforward preparation of thiophthalides **4** by the mean of a one-pot reaction sequence. After some optimization, we could demonstrate that the transiently required phthalides **1f**, **1g** or **1h** could be easily generated *in situ*, in dichloromethane at room temperature, by submitting 2-formyl benzoic acids **5a-c** (1.1 equiv.) to ^{t}BuSH (1 equiv.) in the presence of 0.2 equivalent of $TiCl_4$ and 4Å molecular sieves. Upon the subsequent addition of the desired isocyanide **2** (1.5 equiv.) and extra $TiCl_4$ (2 equiv.), the desired thiophthalides **4** were reliably obtained in respectable yields, for the most identical to those obtained starting directly from *S*-(*t*-butyl)-substituted phthalides (Table 2).

Table 3: One-pot sequential three-component thio-passerini like preparation of carboxamide thiophthalides 4.

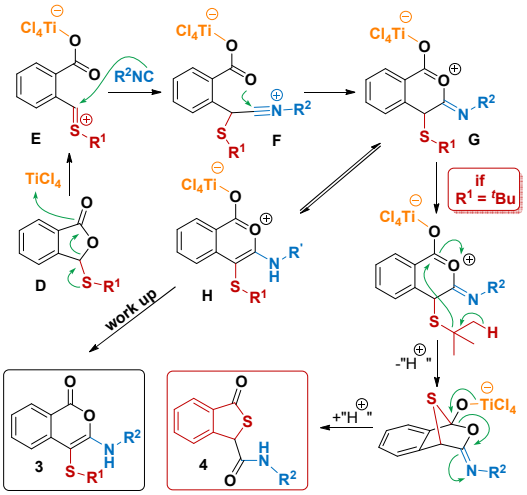


Entry	Substrates	R^1	R^2	**4x**, yield
1	**5a**,**2a**	H	^{t}Bu	**4a**, 69%
2	**5a**,**2b**	H	Cy	**4b**, 78%
3	**5a**,**2c**	H	Bn	**4c**, 58%
4	**5a**,**2d**	H	2,6-$(Me)_2$-C_6H_3	**4d**, 75%
5	**5a**,**2f**	H	2-Napthyl	**4f**, 64%
6	**5a**,**2h**	H	^{n}Pent	**4h**, 79%
7	**5a**,**2i**	H	1,1,3,3-$(Me)_4$-Bu	**4i**, 45%
8	**5a, 2j**	H	-$(CH_2)_2$-3,4-$(MeO)_2$-C_6H_3	**4j**, 58%
9	**5b**,**2b**	Me	Cy	**4b′**, 64%
10	**5c**,**2a**	OMe	^{t}Bu	**4a″**, 72%

Considering the reaction mechanism which may be at stake, as other Lewis acid triggered Passerini couplings,[22] the starting

or the *in situ* generated phthalide **D** is likely activated by $TiCl_4$ to form a transient thiocarbenium **E** which is attacked by the isocyanide. The resulting nitrilium **F** is then trapped intramolecularly by the carboxylate group leading to the oxycarbenium **G**. As witnessed by the typical dark blue-green color of the reaction mixture, a tautomeric equilibrium most probably engenders pyrilium **H**, which relative stability entails the use a stoichiometric amount of $TiCl_4$. Depending on the starting thiol which is used, 3-amino-4-thio-isochromen-1-ones **3** are obtained or, upon higher loading of $TiCl_4$ and the use of ^{t}BuSH, the subsequent thiol dealkylation followed by a Mumm 1,5-acyl transfer promotes the formation of thiophthalides **4**.[19,23]

Scheme 6: Mechanistic proposal



To conclude, we developed two original procedures for the preparation of a large variety of thiophthalides starting from easily accessible sulfanyl-phthalides or directly from the corresponding 2-formyl benzoic acid derivatives. This process, which was proven to implicate the intermediary formation of valuable 4-sulfanyl-isochromenone,[24] features a multi-faceted activity of $TiCl_4$. Formally, these new entries to thiophthalides are based on the coupling between a thiocarbonyl surrogate, an isocyanide and a carboxylic acid and, in so doing, represent the first example of formal thio-Passerini reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, Analytical data, and NMR spectra for all compounds are reported (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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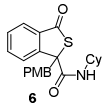
(20) In contrast to what was observed for 4-amino-isochromenones, **3cb** was stable under acidic conditions and did not allow the formation of **4b**, even when submitted to trifluoromethanesulfonic acid (60 mol%) in dichloromethane at room temperature for 2 days.

(21) Starting from the *para*-methoxybenzyl-substituted phthalide **1d**, the formation of **4b** was accompanied with that of compound **6** in 24% yield.



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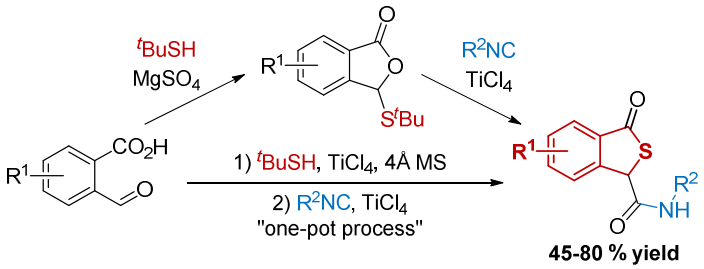

Formal thio-Passerini reactions