

TiCl₄-Mediated Preparation of Thiophthalide Derivatives via Formal Thio-Passerini Reactions

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S Supporting Information

ABSTRACT: By the formal extension of the Passerini reaction to thiocarbonyl derivatives, the straightforward preparation of thiophthalides is disclosed. This method involves the intermediate formation of a sulfanyl-phthalide and a titanium tetrachloride mediated isocyanide insertion reaction. When *tert*-butyl thiol is used, thanks to the deprotection of the *tert*-butyl group, a thiophthalide resulting from a 1,5-Mumm rearrangement is isolated. Owing to the multifaceted activity of TiCl₄, all steps may conveniently be performed in one pot, starting directly from 2-formylbenzoic acids, *tert*-butyl thiol, and various isocyanides.

T hrough 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 of the most studied members 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}

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



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



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 straightforward access to 1,3-dihydro-benzo[c]thiophenone (thiophthalide) derivatives by means of an unprecedented formal thio-Passerini reaction (Scheme 1).^{11,12} Whereas the

Scheme 1. Our Strategy for the Construction of Thiophthaliddes *via* a Thio-Passerini Type Coupling



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

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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).

With this plan in mind, we initially surveyed the practicability of the insertion reaction of isocyanides into an *in situ* generated thiocarbenium \mathbf{A} .^{15,16} For this purpose, 3-phenylsulfanylphthalide $\mathbf{1a}^{17}$ was prepared and submitted to a stoichiometric amount of a variety of Lewis acids in the presence of a slight excess (1.2 equiv) of *tert*-butylisocyanide $\mathbf{2a}$ in dichloromethane at room temperature (Table 1). Among the various Lewis acids

Table 1. Optimization Studies of the Isocyanide Insertion into Thiophthalides

		^t BuNC 2a (1.2 equiv) Lewis Acid (1 equiv)	ρ γ			
		Solvent, 25 °C, time		^t Bu		
	S∼Ph 1a		S ∏ 3aa `Ph			
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	$TiCl(Oi-Pr)_3$	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 ₂ O	$TiCl_4$	1	18		
11	THF	$TiCl_4$	1	0		
12	CH ₃ CN	$TiCl_4$	1	0		
13	Toluene	$TiCl_4$	1	39		
¹ Isolated yield. ^b DCE: 1,2-dichloroethane.						

tested,¹⁸ only two allowed the desired insertion product to be obtained, in the form of the tautomeric thio-isochromenone **3aa** (Table 1, entries 5 and 7). As observed by Chatani and coworkers in the specific context of the isocyanide insertion into symmetrical thioketals, the best yields were achieved using titanium tetrachloride (Table 1, entry 7) but, in opposition to their study, GaCl₃ 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 TiCl₄ 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

With the optimized reaction conditions in hand, sulfanylphthalides 1a and 1b were reacted with a set of several isocyanides (Scheme 2). Remarkably, the 3-amino-4-thio-isochromen-1ones 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-phenylsulfanylphthalide 1a well tolerated the use of either aliphatic or aromatic isocyanide insertion process could straightforwardly be extended to the S-alkyl substituted phthalide 1b. Notably, the reaction Scheme 2. Scope of the TiCl₄-Promoted Isocyanide Insertion into Thiophthalides 1a–b



between **1b** and *tert*-butylisocyanide **2a** afforded the isochromenone **3ba** in a lower 50% yield, as a result of the competitive cleavage of the *tert*-butyl group leading to the corresponding freeamino compound **3ba**' (12% yield).

On the other hand, we were quite pleased to observe that the *S*-cyclohexyl phthalide 1c, in the reaction with 2b, progressed 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 1 equiv of this Lewis acid in dichloromethane at room temperature over a 24-h period (Scheme 3).

To optimize this thio-Passerini-like process and to capitalize on the ability of TiCl₄ 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 2 equiv of TiCl₄ in dichloromethane at room temperature (Table 2). After 2 h, 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 on 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.

 Table 2. Optimization of the S-Protecting Group Allowing the

 Direct Synthesis of Thiophthalides from Phthalides

0 1b-e SR	+ Cy-NC $\xrightarrow{\text{TiCl}_4 (2 \text{ equiv})}{CH_2Cl_2}$ 2b $25^{\circ}\text{C}, 2 \text{ h}$		+ S 4b O NH			
entry	substrate, R	3xx, yield	4b (yield)			
1	1b , ^{<i>n</i>} C ₁₂ H ₂₅	3bb , 93%	-			
2	1c, Cy	3cb, 69%	31%			
3	1 d , PMB ^{<i>a</i>}	3db, 0%	65%			
4	1e, Bn	3eb, 10%	82%			
5	1f, ^t Bu	3fb, 0%	76%			
^{<i>a</i>} PMB = <i>p</i> -methoxybenzyl.						

Conversely, the *p*-methoxybenzyl-, the benzyl-, or the *tert*-butyl-substituted phthalides **1d**, **1e**, and **1f** led straightforwardly to **4b** in 65%, 82%, and 76% yield, respectively.²¹ While the benzyl mercaptan **1e** gave an incomplete conversion, **1f** was selected for the remainder of our studies.

Pleasingly, this direct preparation of thiophthalides 4 from the S-(*tert*-butyl)-substituted phthalide 1f could be efficaciously 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.

To push the boundaries of this formal thio-Passerini process, we envisioned the development of an even more straightforward preparation of thiophthalides 4 by means 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 equiv of TiCl₄ and 4 Å molecular sieves (Table 3). Upon the subsequent addition of the desired

Table 3. One-Pot Sequential Three-Component Thio-Passerini-like Preparation of Carboxamide Thiophthalides 4

	R ¹ 0H 5 a-c (1.1 equiv.)	1) ⁴ TiCl ₄ (0 2) R Tit	BuSH (1 equiv) 2 equiv), 4Å MS, 1h ² NC 2 (1.5 equiv) Cl ₄ (2 equiv), 2h CH ₂ Cl ₂ , rt 4	S NH
entry	substrates	\mathbb{R}^1	R ²	4x , yield
1	5a, 2a	Н	^t Bu	4a, 69%
2	5a, 2b	Н	Су	4b , 78%
3	5a, 2c	Н	Bn	4c , 58%
4	5a, 2d	Н	$2,6-(Me)_2-C_6H_3$	4d , 75%
5	5a, 2f	Н	2-Naphthyl	4f , 64%
6	5a, 2h	Н	"Pent	4h , 79%
7	5a, 2i	Н	1,1,3,3-(Me) ₄₋ Bu	4i , 45%
8	5a, 2j	Н	$-(CH_2)_2$ -3,4-(MeO)_2-C ₆ H ₃	4 j, 58%
9	5b, 2b	Me	Су	4b ′, 64%
10	5c, 2a	OMe	^t Bu	4 a", 72%

isocyanide 2 (1.5 equiv) and extra TiCl₄ (2 equiv), the desired thiophthalides 4 were reliably obtained in respectable yields, comparable to those obtained starting directly from *S*-(*tert*-butyl)-substituted phthalides (Table 2).

Considering the reaction mechanism which may be at stake, as other Lewis acids 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 (Scheme 5). The resulting nitrilium **F** is then trapped

Scheme 5. Mechanistic Proposal



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 pyrylium **H**, in which the relative stability entails the use a stoichiometric amount of TiCl₄. Depending on the starting thiol which is used, 3-amino-4-thio-isochromen-1-ones **3** are obtained or, upon higher loading of TiCl₄ and the use of ^tBuSH, the subsequent thiol dealkylation followed by a Mumm 1,5-acyl transfer promotes the formation of thiophtha-lides **4**.^{19,23}

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 the multifaceted activity of TiCl₄. 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 examples of formal thio-Passerini reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01937.

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

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Notes

The authors declare no competing financial interest.

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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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