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**BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS  
FACULTY OF CHEMICAL AND BIOENGINEERING  
GEORGE OLAH DOCTORAL SCHOOL**

# **Synthesis of Phthalide Building Blocks**

Ph.D. Theses

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**University consultant: Prof. Ferenc Faigl Ph.D., D.Sc.**

**Egis Pharmaceuticals PLC.**

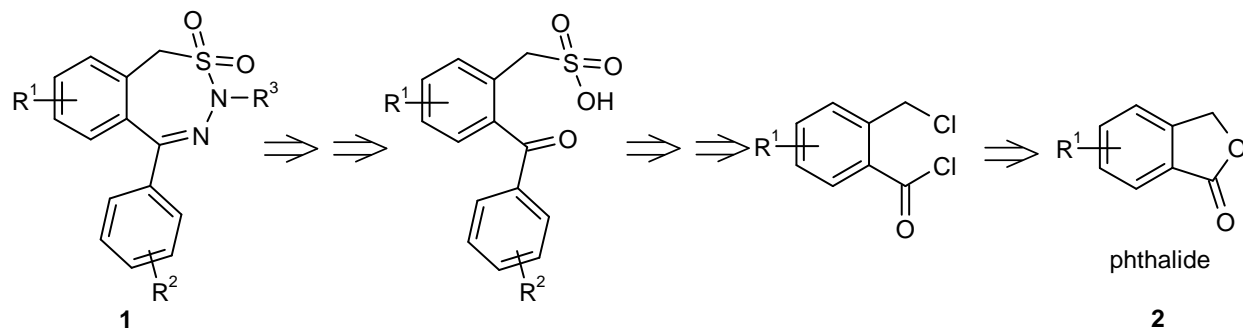
**Chemical Research Division**

**Budapest, 2015**

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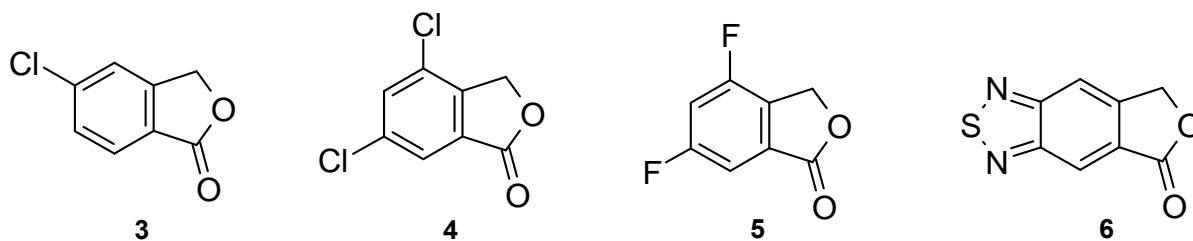
## 1. INTRODUCTION

Search for new compounds structurally related to 2,3-benzodiazepines was an important objective for EGIS R&D. In the course of these efforts, the synthesis of 2,3,4-benzothiadiazepine 2,2-dioxide **1** derivatives was set as a target (Scheme 1).



Scheme 1: The structure of 2,3,4-benzothiadiazepine 2,2-dioxides **1** and their retrosynthetic analysis

Retrosynthetic analysis of *N*(3)-alkyl-2,3,4-benzothiadiazepine 2,2-dioxides (**1**) indicated that suitably substituted phthalides (**2**) were required as starting materials for their synthesis.<sup>1</sup> A new, laboratory scale synthesis of 5-chlorophthalide (**3**, Scheme 2) has been elaborated in the department of Organic Chemistry and Technology in Budapest University of Technology and Economics, at request of EGIS Pharmaceuticals PLC.



Scheme 2: Phthalide target compounds

My task was to elaborate the scaled-up synthesis of 5-chlorophthalide (**3**) and to extend the method for the preparation of the 4,6-dichloro- and 4,6-difluorophthalide (**4** and **5**) which are not known in the literature. In addition, the synthesis of the new thiadiazolophthalide (**6**) was also set as a target of my work.

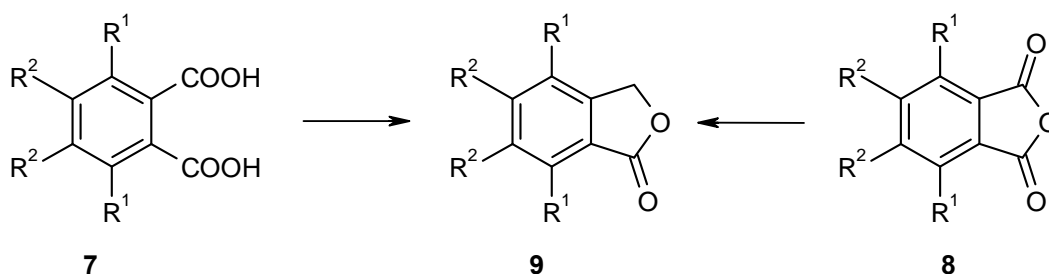
## 2. LITERATURE BACKGROUND OF PHTHALIDES

The phthalides were synthesized by two main methodologies in the literature:

<sup>1</sup> J. Fetter, F. Bertha, B. Molnár, B. Volk, Gy. Simig: *J. Het. Chem.*: DOI 10.1002/jhet.2141

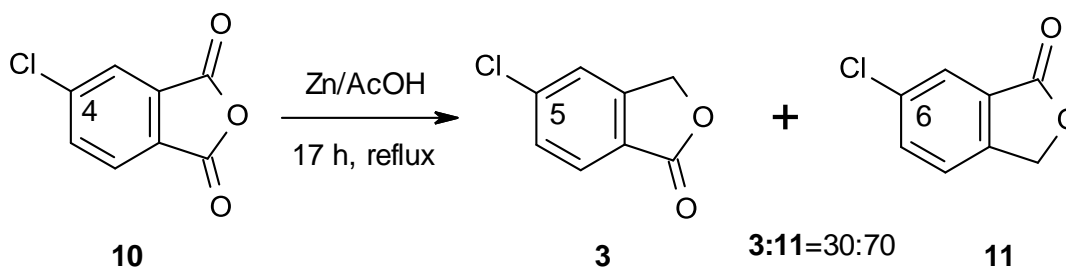
- By reduction of phthalic acid derivatives (phthalic acid, phthalic esters, phthalic anhydride, phthalimide)
- By ring closure of *o*-hydroxymethyl benzoic acids, prepared *via* an *ortho*-lithiation methodology from benzyl alcohols or benzoic acid derivatives

**2.1.** The reduction of symmetrically substituted phthalic acids (**7**) and phthalic anhydrides (**8**) by various reducing agents led to **9** phthalides in good yields (Scheme 3).<sup>2</sup>



Scheme 3: Reduction of symmetrically substituted phthalic acids (**7**) and phthalic anhydrides (**8**)

The reduction of asymmetrically substituted phthalic anhydrides, as demonstrated by the example of 4-chlorophthalic anhydride (**10**, Scheme 4), led to a mixture of phthalides (**3**, **11**). Therefore, this is not an efficient method for the synthesis of the required 5-chlorophthalide (**3**).<sup>3</sup>

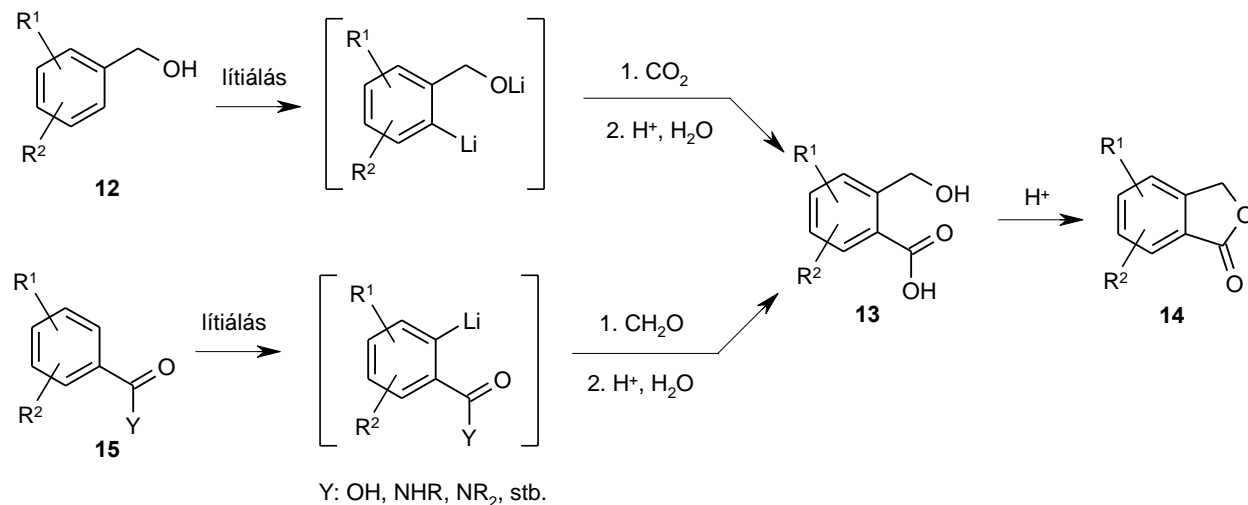


Scheme 4: Reduction of 4-chlorophthalic anhydride (**10**)

**2.2.** *Ortho*-lithiation of benzyl alcohols (**12**) and subsequent carboxylation led to *o*-hydroxymethyl-benzoic acids (**13**) and their acid-catalyzed ring closure gave phthalides (**14**, Scheme 5). This method is strongly limited by the poor *ortho*-directing effect of the hydroxymethyl group in lithiation reactions. *Ortho*-lithiation of benzoic acid derivatives (**15**) and subsequent hydroxymethylation is the more frequently applied approach for the synthesis of *o*-hydroxymethylbenzoic acid derivatives (**13**), which affords phthalides (**14**) after acidic treatment. It is interesting to mention that formylation of *ortho*-lithio benzoic acid derivatives and subsequent reduction gives compounds **13** in much better yields than the direct hydroxymethylation with formaldehyde.

<sup>2</sup> Z.-L. Zhou, S. M. Kher, S. X. Cai, E. R. Whittemore, S. A. Espitia, J. E. Hawkinson, M. Tran, R. M. Woodward, E. Weber, J. F. W. Keana; *Bioorg. Med. Chem.* **2003**, *11*, 1769–1778

<sup>3</sup> P. Nandhikonda, M. D. Heagy; *Org. Lett.* **2010**, *12*, 4796–4799



Scheme 5: Syntheses of phthalides *via ortho*-lithiation

### 3. EXPERIMENTAL METHODS

During the synthetic work, well known methods of preparative organic chemistry were applied. The progress of reactions was followed by thin layer chromatography. The crude products were purified by recrystallization or by trituration with various solvents. The isomeric ratios were determined by GC-MS technique. The melting points of solid compounds were determined. The structures of compounds were identified by <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and IR spectra, and the purity was also demonstrated by elemental analysis. The structure of one compound was determined by single crystal X-Ray diffraction measurement.

## 4. RESULTS

### 4.1. Scaled-up synthesis of 5-chlorophthalide<sup>4</sup>

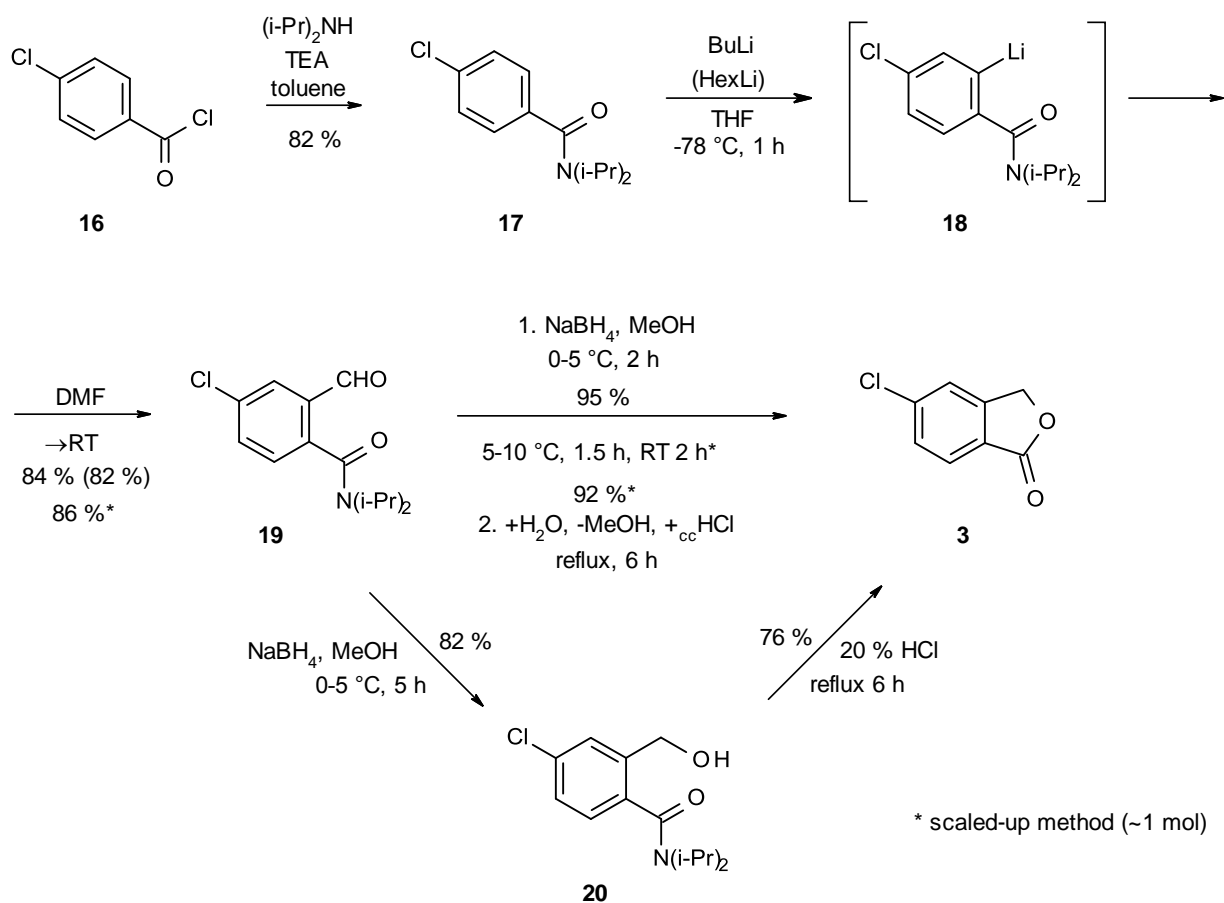
Preceding my work, Professor Dr. Ferenc Faigl and his research group (at the Department of Organic Chemistry and Technology at the Budapest University of Technology and Economics) have elaborated a laboratory synthesis of 5-substituted phthalides (including 5-chlorophthalide) at the request of EGIS Pharmaceuticals PLC.

4-Chloro-*N,N*-diisopropylbenzamide (**17**), obtained by amidation of 4-chlorobenzoyl chloride, (**16**) with diisopropyl-amine was lithiated with butyllithium in the *ortho* position of the amide

<sup>4</sup> F. Faigl, A. Thurner, B. Molnár, Gy. Simig, B. Volk; *Org. Proc. Res. Dev.* **2010**, *14*, 617–622

group (**18**) and formylated (**19**, Scheme 6, the yields indicated on Scheme 6 are those of the scaled-up method). Aldehyde **19** thus obtained was reduced by sodium borohydride to hydroxymethyl derivative **20**, which was converted into phthalide **3** by refluxing in aqueous hydrochloric acid.

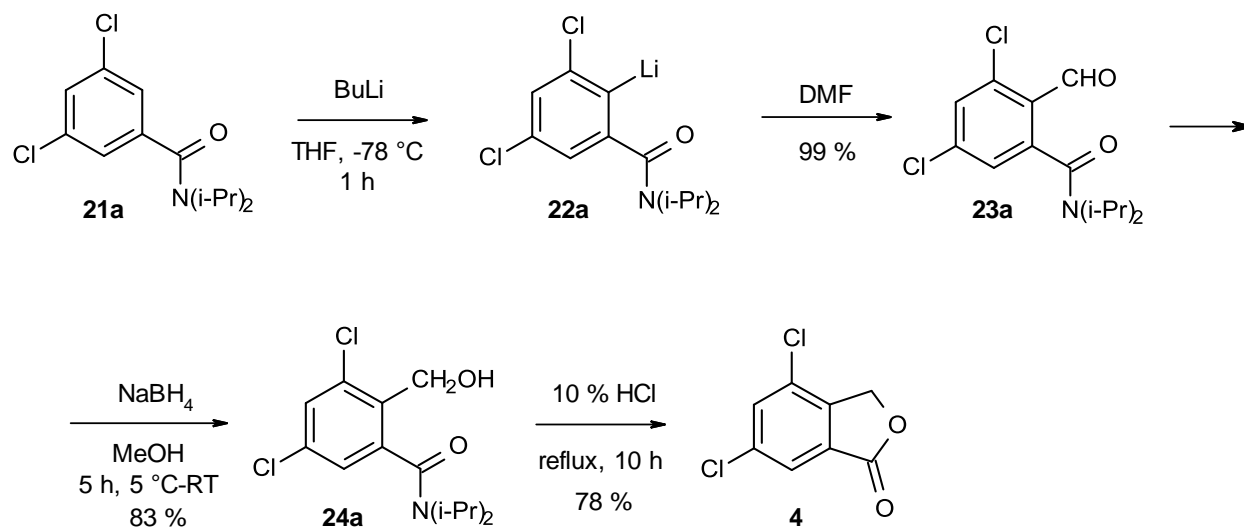
In the course of scaling up, industrial expectations were also considered. The purifications of intermediates were modified (suspending vs. recrystallization). The industrially undesirable solvents were avoided (e.g. diethyl ether, dichloromethane). A technologically simple, environment-friendly one-pot methodology has been developed for the formation of 5-chlorophthalide from 4-chloro-2-formyl-*N,N*-diisopropylbenzamide (**19**) in high yield. It was confirmed that butyllithium can be replaced with the technologically more advantageous hexyllithium in the lithiation step. The overall yield of the scaled-up technology has been increased from 51 % of the laboratory scale synthesis to 79 %.



Scheme 6: The scaled-up synthesis of 5-chlorophthalide

## 4.2. Synthesis of 4,6-dichloro- and 4,6-difluorophthalide<sup>5</sup>

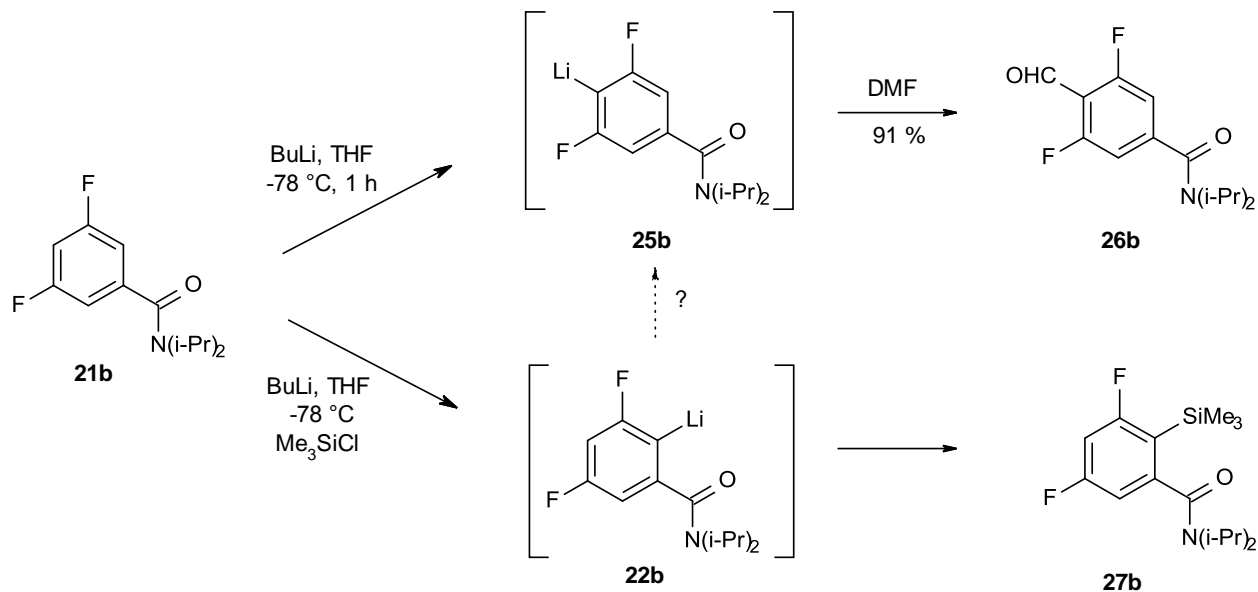
We have planned to synthesize 4,6-dichlorophthalide and 4,6-difluorophthalide (**4**, **5**) analogously to the synthesis of 5-chlorophthalide. Lithiation of 3,5-dichloro-*N,N*-diisopropylbenzamide (**21a**) was carried out under the same conditions as the lithiation of 4-chloro-*N,N*-diisopropylbenzamide (**17**). Subsequent formylation with DMF gave 4-chloro-2-formyl-*N,N*-diisopropylbenzamide (**23a**) in 99 % yield (Scheme 7). The lithiation occurred at the *ortho* position of the amide moiety (**22a**). Phthalide **4** could be synthesized from formyl derivative **23a** as usual.



Scheme 7: Synthesis of 4,6-dichlorophthalide (**4**)

Surprisingly, lithiation of 3,5-difluoro-*N,N*-diisopropylbenzamide (**21b**) under the same conditions as above and subsequent reaction with DMF gave 4-formyl isomer **26b** in 91 % yield (Scheme 8).

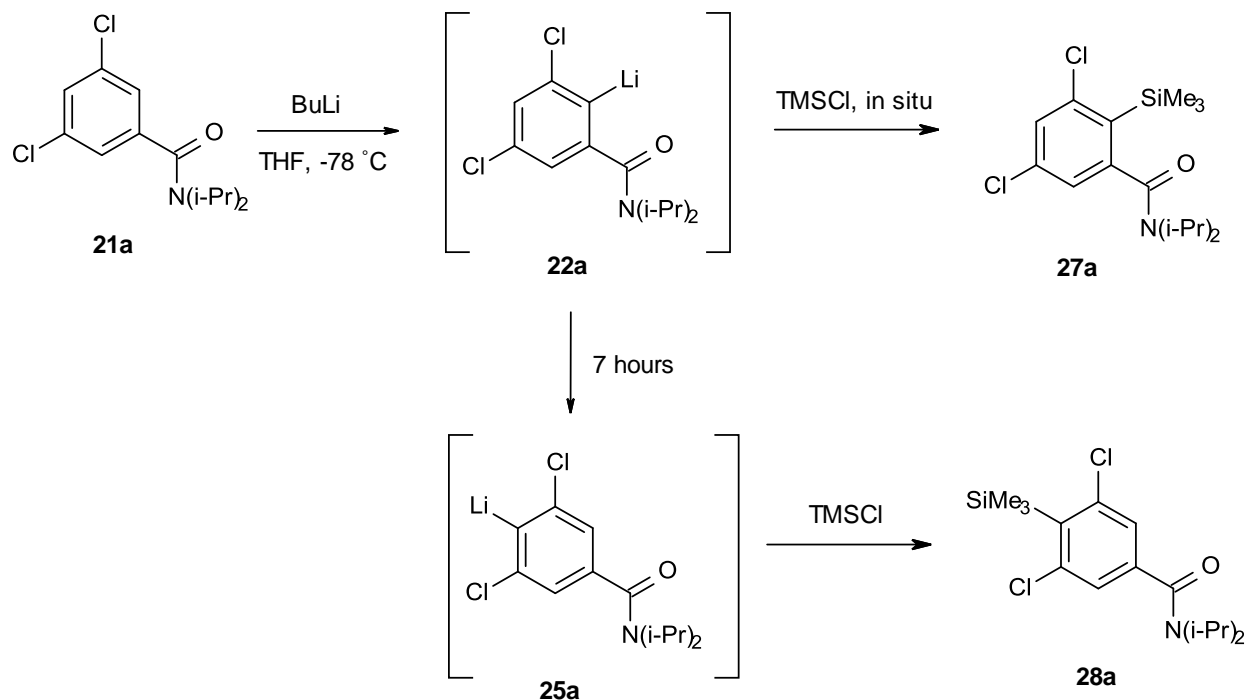
<sup>5</sup> B. Molnár, Gy. Simig, B. Volk; *Eur. J. Org. Chem.* **2011**, 1728–1735



The formation of formyl derivative **26b** can be explained by two different ways. The first possibility is that 3,5-difluoro-*N,N*-diisopropylbenzamide (**21b**) was lithiated directly at position 4 (**25b**) and subsequent reaction with DMF resulted in 4-formyl derivative **26b**. The other possibility is that the lithiation occurred at position 2 (**22b**, kinetically controlled product) and the initially formed lithio intermediate isomerized to the 4-lithio derivative (**25b**, thermodynamically controlled product) resulting in formyl derivative **26b** after treatment with DMF. It has been confirmed by in situ trapping with  $\text{TMSCl}$ <sup>6</sup> that under the applied reaction conditions 3,5-difluoro-*N,N*-diisopropylbenzamide (**21b**) was initially lithiated at position 2. Thus **22b** is the kinetically favoured product, which isomerized to the thermodynamically stable (less basic) 4-lithio derivative **25b**.

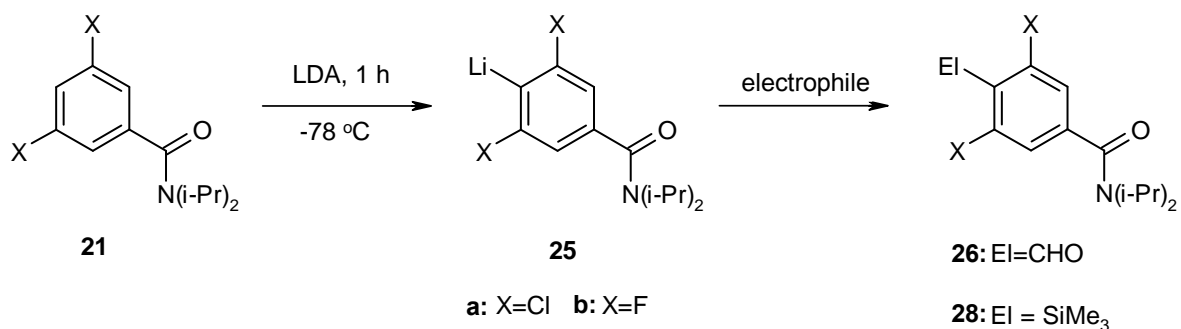
After that, the question arised whether the 2-lithio derivative obtained by lithiation of 3,5-dichloro-*N,N*-diisopropylbenzamide (**21a**) was a kinetically or a thermodynamically favoured product. The lithiation was performed in the presence of  $\text{TMSCl}$ , which resulted in 3,5-dichloro-2-(trimethylsilyl)benzamide (**27a**, Scheme 8) in 88 % yield. However, lithiation of 3,5-dichlorobenzamide **21a** with butyllithium for 7 hours at  $-78\text{ }^\circ\text{C}$  followed by treatment with  $\text{TMSCl}$  resulted in 4-TMS derivative **28a** in 83 % yield, indicating that the kinetically formed 2-lithio derivative **22a** rearranged to the thermodynamically more stable 4-lithio derivative **25a** in this case as well.

<sup>6</sup> S. Caron, J. M. Hawkins; *J. Org. Chem.* **1998**, *63*, 2054–2055



Scheme 8: Lithiation reaction of **21a**

It is known that the lithiating agent LDA in most cases abstracts the proton from the most acidic site of the substrates,<sup>7</sup> and leads to the thermodynamically more stable lithio derivative directly.<sup>8</sup> Treatment of benzamides **21a** and **21b** with LDA at  $-78\text{ }^{\circ}\text{C}$  in THF for 1 hour and subsequent reaction with TMSCl or DMF afforded 4-substituted derivatives **26** and **28** in good yields (Scheme 9).

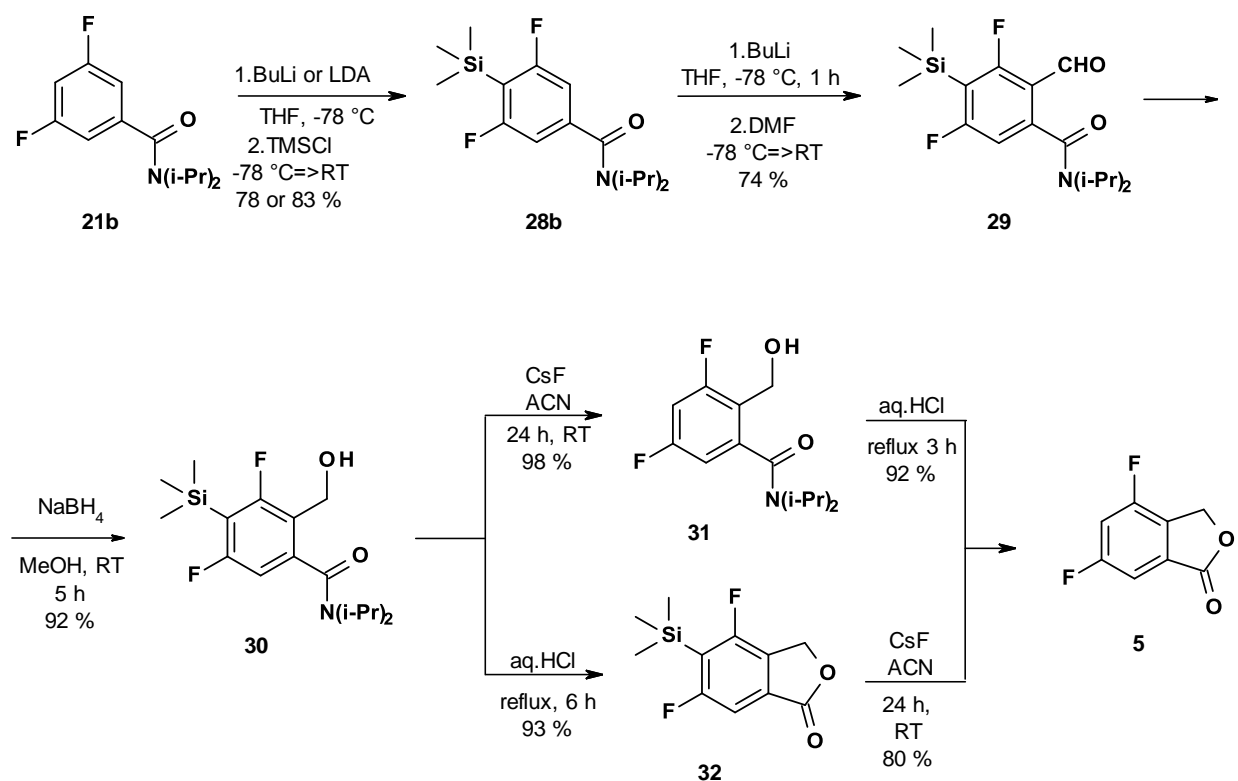


Scheme 9: Lithiation of **21a** and **24b** using LDA base

<sup>7</sup> M. Dabrowski, J. Kubicka, S. Lulinski, J. Serwatowski; *Tetrahedron Lett.* **2005**, *46*, 4175–4178

<sup>8</sup> F. Mongin, M. Schlosser; *Tetrahedron Lett.* **1997**, *38*, 1559–1562

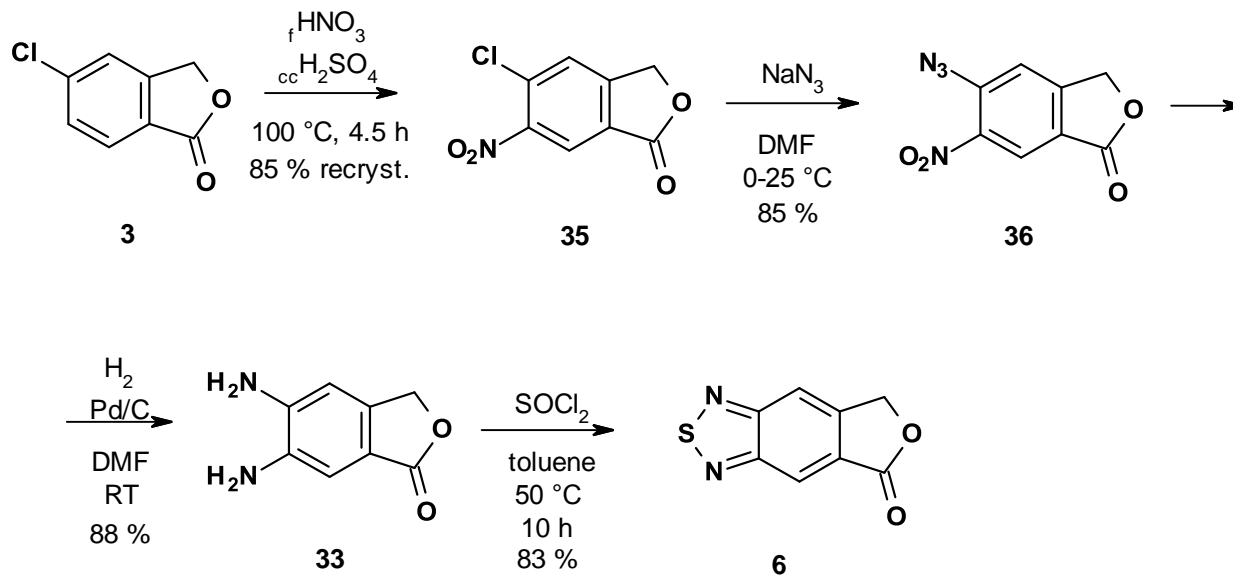
After the results shown above we came to the conclusion that the synthesis of phthalide **5** starting from 3,5-difluorobenzamide **21b** could be performed only if the position 4 is protected (Scheme 10). Trimethylsilyl group was selected as protecting group, because it is intact during the second lithiation step and can be easily removed. Lithiation of 3,5-difluoro-*N,N*-diisopropylbenzamide (**21b**) was performed at  $-78\text{ }^{\circ}\text{C}$  in THF using butyllithium or LDA. After quenching with TMSCl, benzamide **28b** was obtained in 78 and 83 % yield, respectively. Lithiation of benzamide **28b** with butyllithium followed by reaction with DMF gave formyl derivative **29** in 74 % yield, which was reduced to hydroxymethyl derivative **30** with sodium-borohydride in methanol in 92 % yield.



Scheme 10: Synthesis of 4,6-difluorophthalide (**5**)

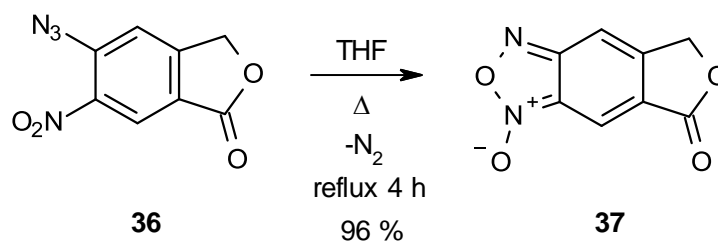
The synthesis was continued via two routes: the protecting group was removed before (**31**) or after (**32**) the ring closure. The yield was slightly better in the case when deprotection was applied from derivative **30**. The 4,6-difluorophthalide was synthesized in 5 steps, in 51 % total yield based on 3,5-difluorobenzamide **21b**.





Scheme 12: New synthesis of 5,6-diaminophthalide (**33**) and thiadiazolophthalide (**6**)

In the course of recrystallization of 5-azido-6-nitrophthalide (**36**), the intermediate of our diaminophthalide (**33**) synthesis, its thermal lability was observed. Recrystallization of compound **36** from ethanol or THF gave a new compound. Its structure has been determined by single crystal X-ray diffraction measurement. The thermal rearrangement of 5-azido-6-nitrophthalide resulted in 5*H*,7*H*-furo[3,4-*f*][2,1,3]benzoxadiazole-5-one 3-oxide (**37**) which is not known in the literature (Scheme 13).



Scheme 13: Thermal rearrangement of azido-nitrophthalide **36**

## 5. THESES

1. A new scaled-up method has been elaborated for the synthesis of 5-chlorophthalide starting from 4-chloro-*N,N*-diisopropylbenzamide. The key step was a directed *ortho*-metallation of the benzamide at position 2, followed by formylation. In the course of scaling up, industrial expectations were also considered. The purifications of the intermediates were simplified, the industrially undesirable solvents were avoided. A technologically streamlined, environment-friendly one-pot methodology has been developed for the synthesis of 5-chlorophthalide from 4-chloro-2-formyl-*N,N*-diisopropylbenzamide in high yield.<sup>4</sup>

2. A new procedure was elaborated for the synthesis of 4,6-dichloro- and 4,6-difluorophthalides, which are not known in the literature, starting from the appropriate 3,5-dihalogeno-*N,N*-diisopropylbenzamides. The key step was a directed *ortho*-metallation of the benzamides at position 2, followed by formylation. It was demonstrated that lithiation of both 3,5-dichloro- and 3,5-difluoro-*N,N*-diisopropylbenzamide with butyllithium occurred at position 2, however, the primarily formed, kinetically controlled 2-lithio derivatives isomerized, with very different reaction rates, to the thermodynamically controlled 4-lithio derivatives.<sup>5</sup>

3. I found that lithiation of 3,5-dichloro-*N,N*-diisopropylbenzamide with butyllithium for 1 hour followed by reaction with DMF afforded 2-formyl derivative in excellent yield, whereas after 7 h lithiation time the corresponding 4-formyl derivative was obtained in good yield. I demonstrated that lithiation of 3,5-difluoro-*N,N*-diisopropylbenzamide with butyllithium primarily occurred in the position 2, however, the 2-lithio derivative underwent an extremely fast isomerisation to the 4-lithio isomer. Consequently, the introduction of formyl group via *ortho*- lithiation to position 2 of 3,5-difluoro-*N,N*-diisopropylbenzamide could be achieved after protection of position 4. Therefore, the synthesis of 4,6-difluorophthalide could be performed only with temporary protection of position 4. Starting from the 3,5-dihalogeno-*N,N*-diisopropylbenzamide, 4,6-dichlorophthalide was synthesized in 3 steps and 4,6-difluorophthalide was synthesized in 5 steps in good overall yields.<sup>5</sup>

4. A new, efficient synthesis of 5,6-diaminophthalide was elaborated starting from 5-chlorophthalide. It was found that the 5-azido-6-nitrophthalide intermediate of our synthesis rearranged into the corresponding oxadiazole-*N*-oxide upon heating. Starting from 5,6-diaminophthalide, the thiadiazolophthalide, which is not known in the literature, was synthesized in high yield. Thiadiazolophthalide is a versatile scaffold to access a wide range of condensed heterocyclic ring systems.<sup>9,1</sup>

## 6. PUBLICATIONS

### 6.1. Publications related to the PhD thesis

- › Ferenc Faigl, Angelika Thurner, Balázs Molnár, Gyula Simig, Balázs Volk: **Manufacturing Synthesis of 5-Substituted Phthalides**; *Organic Process Research & Development* 2010. 14, 617–622. [IF.: 2,207 (2010)]
- › Balázs Molnár, Gyula Simig, Balázs Volk: **Synthesis of 4,6-Dichloro- and 4,6-Difluorophthalides: a Systematic Study on the Lithiation of 3,5-Dihalo-*N,N*-diisopropylbenzamides**; *European Journal of Organic Chemistry* 2011. 1728–1735. [IF: 3,329 (2011)]
- › Balázs Molnár, Gyula Simig, Tibor Bakó, András Dancsó, Balázs Volk: **Efficient syntheses of the versatile phthalide building blocks, 5,6-diaminoisobenzofuran-1(3*H*)-one and 5*H*,7*H*-furo[3,4-*f*][2,1,3]benzothiadiazol-5-one**; *Tetrahedron Letters* 2012. 53, 2922–2924. [IF: 2,397 (2012)]
- › József Fetter, Ferenc Bertha, Balázs Molnár, Balázs Volk, Gyula Simig: **Chemistry of an unexplored heterocyclic ring system: versatile synthesis of 5-aryl-2,3,4-benzothiadiazepine 2,2-dioxides**; *Journal of Heterocyclic Chemistry: DOI 10.1002/jhet.2141*. [IF: 1,224 (2013)]

### 6.2. Presentations related to the topics of the PhD thesis

- › Balázs Molnár, Ferenc Faigl, Angelika Thurner, József Fetter, Ferenc Bertha, Gyula Simig: **New Syntheses of New Phthalides**; XXth International Symposium on Medicinal Chemistry, Vienna, Austria, 2008. (Poster)
- › Balázs Molnár, Ferenc Faigl, Angelika Thurner, József Fetter, Ferenc Bertha, Gyula Simig: **Új ftalidok szintézise (Syntheses of new phthalides)**; Annual Meeting on Heterocycles of the working committee of the Hungarian Academy of Sciences,, Balatonszemes, 2009. (Oral presentation)
- › Balázs Molnár, Gyula Simig: **Kinetikus és termodinamikus kontroll aromás lítiálási reakciókban (Role of kinetic and thermodynamic control over lithiation reactions of aromatics)**; Annual Meeting on Heterocycles of the working committee of the Hungarian Academy of Sciences, Balatonszemes, 2010. (Oral presentation)
- › Balázs Molnár, Gyula Simig, József Fetter, Ferenc Bertha: **2,3,4-Benzothiadiazepin-2,2-dioxid származékok szintézise (Syntheses of 2,3,4-benzothiadiazepine 2,2-dioxides)**; Annual Meeting on Heterocycles of the working committee of the Hungarian Academy of Sciences, Balatonszemes, 2011. (Oral presentation)

### 7.3. Other publications

- › Gyula Simig, József Fetter, Ferenc Bertha, Ferenc Faigl, Angelika Thurner, Balázs Molnár, József Barkóczy, Balázs Volk.: **2,3,4-Benzothiadiazepin-2,2-dioxid származékok szintézise (Synthesis of 2,3,4-benzothiadiazepine-2,2-dioxides)**; *Magyar Kémikusok Lapja* **2012**, 67, 38–39.
- › József Fetter, Ferenc Bertha, Balázs Molnár, Gyula Simig, József Barkóczy, Balázs Volk, György Lévyay, István Gacsályi, Gábor Gigler, Hajnalka Kompagne, Bernadett Markó, Katalin Nagy, Péter Kiricsi, Gábor László Hársing, Gábor Szénási: **2,3,4-Benzothiadiazepine-2,2-dioxide derivatives**; WO 2011/039554.

### 7.4. Other presentation

- › Márta Porcs-Makkay, Tibor Mezei, Gyula Simig, Balázs Molnár: **Synthesis of 3-nitroanthranilic acid derivatives**; 13<sup>th</sup> FEICHEM Conference on Heterocycles in Bioorganic-Chemistry, Sopron, 2006. (Poster, English)