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Tandem reversible addition–intramolecular lactonization for the synthesis of 3-functionalized phthalides

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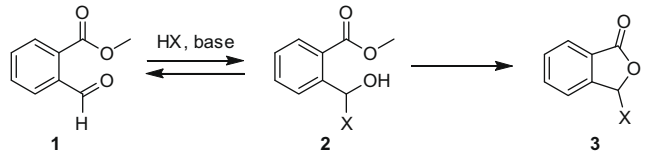
ABSTRACT

A new tandem process based on reversible nucleophilic addition and intramolecular lactonization of methyl 2-formylbenzoate leads to the efficient synthesis of 3-functionalized phthalides, which are important precursors for the synthesis of quinone skeletons via Hauser–Kraus annulation. The reactions are successfully carried out under mild conditions in single operations.

Reversible chemical phenomena constitute a class of essential fundamental reactions in chemistry. A key feature of these reactions is their sensitivity to changes in the reaction conditions such as temperature, pressure, and pH, resulting in control of the equilibrium displacement that potentially leads to enhanced formation of desired products. Numerous applications of reversible reactions, both covalent and non-covalent bond formation, have been reported in many areas.[1–5] Highly intriguing applications are one-pot multi-step reactions, in which several transformations are combined in a one-pot process without isolating any intermediates. This cascade- or tandem strategy is very useful for decreasing the number of synthetic steps and increasing the product yield as well as the efficiency of the process.[6–8]

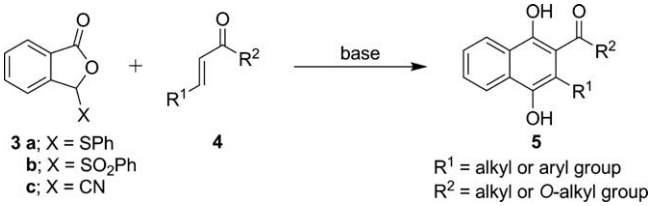
We recently reported an efficient, stereoselective tandem nitroaldol-lactamization concept for kinetic resolution of complex dynamic nitroaldol systems.[9,10] In this case, the reversible nitroaldol process was used to generate a library of nitroaldol adducts, which subsequently was resolved when certain species underwent cyclization and an irreversible intramolecular rearrangement leading to 3-substituted isoindolin-1-one products. In the present study, a new synthetic methodology for generating functionalized phthalides has been developed involving base-catalyzed tandem nucleophilic addition–lactonization in a single operation (Scheme 1). The base-catalyzed reversible reaction between an aldehyde **1** and a nucleophile generated alcohol intermediate **2**, which spontaneously lactonized to produce a 3-substituted phthalide product **3**.

The 3-functionalized phthalides **3** are important key precursors for the synthesis of quinone skeletons which form core structures of quinoid natural products,[11–13] and are the basis of disperse anthraquinone dyes.[14] Although there are a variety of strategies for the synthesis of quinones,[15–17] phthalide annulation is an especially useful methodology resulting in a facile, one-pot process. This annulation reaction was originally developed in the late 1970s by Hauser and Kraus,[18,19] where phthalides **3** (Hauser–Kraus donors) were reacted with Michael acceptors **4**, under strongly basic conditions, generating substituted naphthalene products **5** (Scheme 2).



Scheme 1. Base-catalyzed tandem reversible nucleophilic addition–lactonization.

A variety of substituted quinone skeletons for highly substituted natural product synthesis can be prepared using phthalide derivatives **3**, and also those having different substitution patterns on the aromatic ring. The aromatic substituents on phthalide **3**, however, affect the regioselectivity in annulated product formation. The 3-position of Hauser–Kraus annulation donors **3** has been investigated thoroughly for many functional groups, including phenylsulfanyl, phenylsulfonyl, cyano, methoxyester, phosphonyl groups, etc.[20–22] These functional groups were primarily evaluated for enhancing the acidity of the benzylic protons, for stabilizing the



Scheme 2. Hauser–Kraus annulation.

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formation of the anion, and also for acting as good leaving groups in the annulation reaction. Many efforts have been reported where the functional groups of different functionalized phthalides have been evaluated with respect to electron-withdrawing ability in comparison to annulation reactivities under basic conditions.[23,24]

Although the functionalized phthalides **3a–c** are the most commonly used precursors in Hauser–Kraus annulations, there are only a few reports of synthetic modifications of these compounds.[18,19,25,26] In the present study, a new synthetic strategy is proposed for efficient formation of phthalides **3a** and **3c**. In this strategy, the advantage of using multi-step reactions of combined reversible- and irreversible processes in a single operation have been explored. The key to this strategy is the base-catalyzed generation of alcohol intermediates **2** from the reversible reactions of nucleophiles with benzaldehyde **1**. Adducts **2** subsequently underwent spontaneous lactonization to produce stable phthalide products **3a** and **3c**, all under very mild reaction conditions.

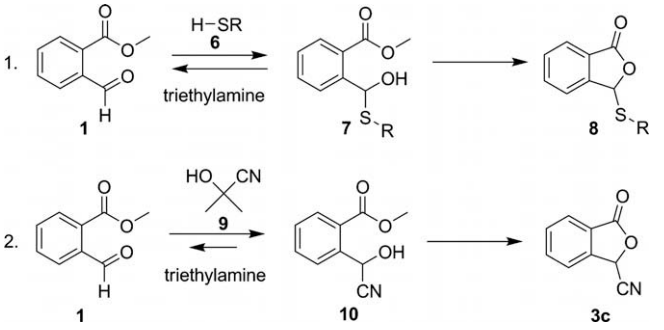
Organosulfur compounds play an important role in organic synthesis, in part due to the fact that sulfur groups can stabilize carbanion formation, and serve as good leaving groups.[27] Phthalides **3a** and **3b** provide excellent demonstrations of these effects. These precursors are commonly used in Hauser–Kraus annulation reactions because both phenylsulfanyl and phenylsufonyl groups act as good stabilizing and leaving groups. However, there have been only a few attempts made to modify the sulfur moiety in the 3-thiophthalide building blocks.[18,26,27] To overcome these limitations, a new series of 3-thiophthalides were prepared successfully using a large range of different thiols. Furthermore, 3-cyanophthalide **3c**, one of the most frequently used donors in the Hauser–Kraus annulation, has also been prepared using the same synthetic concept. The results are summarized in Table 1.

During the synthesis of 3-thiophthalides **8**, the reversible reactions between benzaldehyde **1** and the thiols **6** were initially investigated in the presence of a variety of catalysts, including bases, and Brønsted and Lewis acids. The reaction worked well with a catalytic amount of triethylamine and generated the hemithioacetal intermediates **7** which lactonized to afford the 3-thiophthalides **8**. However, dithioacetals were also formed as by-products in low amounts. The amount of triethylamine was further optimized to avoid dithioacetal formation while still enhancing the reaction rate. Subsequently, the reactions of a series of aliphatic and aromatic thiols, including thiols containing other functional groups were investigated using the optimized reaction conditions. Isolation of pure products was easily accomplished by flash chromatography.

The formation of 3-thiophthalides based on short aliphatic thiols has not been reported because the reaction conditions were not suitable for thiols with lower boiling points.[18,19,26,27] In our strategy, reactions of thiols **6a–f** containing linear (entries 1 and 2), branched (entries 3, 4, and 6), and cyclic (entry 5) aliphatic structures, however, successfully generated the corresponding products **8a–f**. The primary aliphatic thiols **6a–c** gave phthalides **8a–c** in less than 5 h. As expected, the steric hindrance of the secondary and tertiary thiols **6d–f** affected unfavorably the formation of products 8d–**f**, which displayed slow reaction rates of 12, 13, and 48 h, respectively.

Modification of the aromatic thiol part in 3-sulfanylphthalides has been studied,[28] and a moderately electron-releasing methyl substituent in the *para*-position of the aromatic thiol moiety resulted in smooth Hauser–Kraus annulation to afford the corresponding annulated product in high yield. To further expand the scope of the donor properties, 3-thiophthalides based on aromatic thiols **6g–j** were evaluated (entries 7–10). Thiophenol **6g**, thionaphthol **6j**, and 3-methoxythiophenol **6h**, bearing an electron-releasing group, thus formed the corresponding products in 4–5 h, whereas 4-trifluoromethylthiophenol **6i** formed the corresponding product **8i** in a longer reaction time (46 h, entry 9). Furthermore, thiols

Table 1
Synthesis of 3-thiophthalides **8** and 3-cyanophthalide **3c**



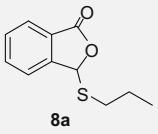
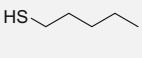
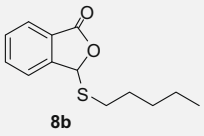
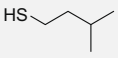
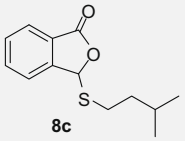
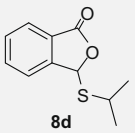
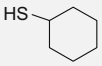
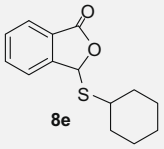
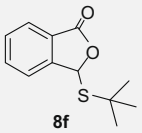
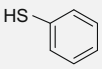
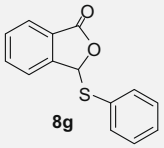
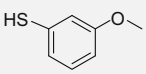
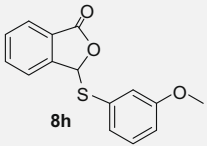
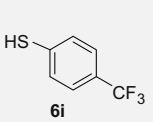
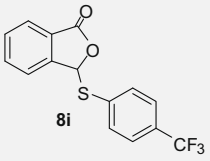
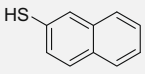
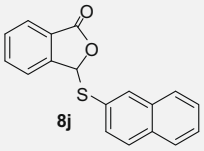
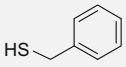
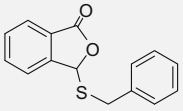
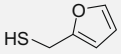
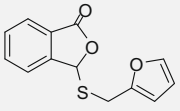
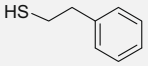
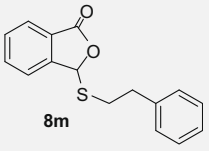
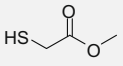
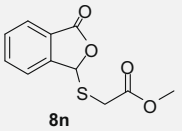
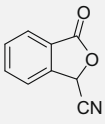
Entry	Nucleophile	Product	Time[a] (h)
1	 **6a**	 **8a**	5
2	 **6b**	 **8b**	4
3	 **6c**	 **8c**	4
4	 **6d**	 **8d**	12
5	 **6e**	 **8e**	13
6	 **6f**	 **8f**	48
7	 **6g**	 **8g**	4
8	 **6h**	 **8h**	4

Table 1 (*continued*)

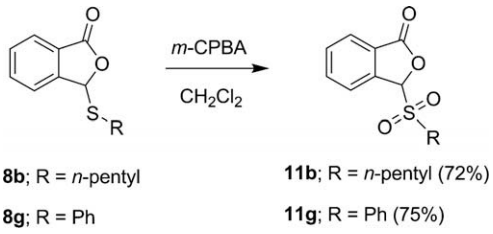
Entry	Nucleophile	Product	Time[a] (h)
9	 **6i**	 **8i**	46
10	 **6j**	 **8j**	5
11	 **6k**	 **8k**	3
12	 **6l**	 **8l**	7
13	 **6m**	 **8m**	5
14	 **6n**	 **8n**	8
15	 **9**	 **3c**	—[b]

[a] Reagents and conditions: benzaldehyde **1** (0.25 mmol), thiol **6** (1.25 mmol), triethylamine (2.5 mmol) in $CDCl_3$ (0.5 mL). After benzaldehyde **1** was converted into phthalide product at >95% conversion (^{1}H NMR), all products were purified by flash chromatography (hexane/CH_2Cl_2 1:1, v/v) giving 80–93% isolated yield.

[b] For 3-cyanophthalide **3c** formation, the mixture of benzaldehyde **1** (0.25 mmol), acetone cyanohydrin **9** (0.37 mmol), and triethylamine (0.02 mmol) in chloroform (2 mL) was stirred at room temperature overnight and then at 0 °C until benzaldehyde **1** has been completely consumed.

6k–n containing aromatic moieties (entries 11–13) and ester groups yielded products **8k** and **8m** in only three and 5 h, respectively. In thiols **6l** and **6n**, the nucleophilicity at sulfur was reduced by the furan and ester moieties, leading to slow formation of phthalide products **8l** and **8n** in 7 and 8 h, respectively.

In addition to the thiol nucleophiles, formation of 3-cyanophthalide **3c** was also investigated using the same concept. Reversible cyanohydrin reaction under basic conditions was thus used, coupled with a secondary lactonization reaction. Acetone cyanohydrin **9** was chosen as the cyanide source because it releases cyanide ions, and acetone as a by-product, under mild reaction conditions.[29] Applying the same reaction conditions as for 3-thiophthalides **8**, however, resulted in degradation of the cyanohydrin intermediate **10** upon precipitation of the triethylammonium cyanide salt. Decreasing the amount of triethylamine to 1 equiv solved this problem, but instead resulted in formation of the dimerized phthalide as the major product.[27] After further optimization, the preparation of 3-cyanophthalide **3c** was successfully accomplished in the presence of a catalytic amount of triethylamine at 0 °C. Purification by flash chromatography afforded 3-cyanophthalide **3c** in 55% yield.[30]



Scheme 3. Formation of sulfone products **11b** and **11g**.

Finally, the possibility to convert 3-thiophthalides **8** into the corresponding sulfones, which are known to be good Hauser–Kraus donors, was demonstrated. 3-Phenylthiophthalide **8g** and 3-pentylthiophthalide **8b** were subjected to oxidation with 5 equiv of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane to afford the corresponding sulfone products **11b** and **11g** in good yields (Scheme 3).

In this study, a powerful tandem reaction has been developed for the synthesis of 3-functionalized phthalides, which are useful synthons for the preparation of quinone skeletons. The strategy is based on a combination of reversible alcohol formation under mildly basic reaction conditions, followed by spontaneous lactonization, all in a single operation. A new series of 3-thiophthalides were formed using this strategy. Oxidation of the 3-thiophthalides gave 3-sulfonylphthalides for Hauser–Kraus annulations.

As expected, the reaction kinetics of thiophthalide formation was found to be influenced by the structures and reactivities of the corresponding thiols. Reactions between benzaldehyde **1** and a series of aliphatic thiols, including linear, branched, and cyclic structures, all successfully produced 3-thiophthalides, whereas, steric effects retarded phthalide formation. For aromatic thiols, substituent effects were investigated, and the reaction of thiophenols with electron-releasing groups accelerated the reaction rate. Aliphatic thiols carrying aryl and ester groups were also evaluated.

Furthermore, 3-cyanophthalide **3c** was successfully formed in high yield using the same synthetic methodology. The reversible cyanohydrin reaction using acetone cyanohydrin in the presence of a catalytic amount of base at low temperature was utilized to produce the 3-cyanophthalide product.

Acknowledgments

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Supplementary data

Supplementary data (characterization data of phthalides **3a–c**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.079.

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30. See Supplementary data for additional information.