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Stereoselective Synthesis of Alkylidene Phthalides

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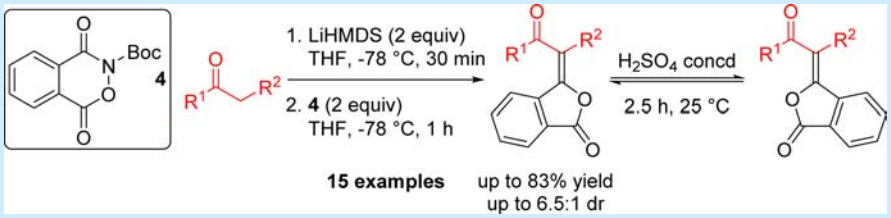
Supporting Information



ABSTRACT: The *N*,*O*-diacylhydroxylamine derivative **4** has been prepared and its reactivity with nucleophiles investigated. On reaction with lithium enolates of cyclic or acyclic ketones, **4** is converted stereoselectively to the corresponding alkylidene phthalide. The stereochemical outcome of the transformation can be modified by changing the polarity of the reaction medium and the products isomerized under acidic conditions.

Natural products frequently provide the inspiration for pioneering work in drug discovery and synthesis.[1] Uncovering new routes to prepare privileged fragments of biological importance[2] is therefore of great interest and delivers a motivation for methodology development.[3] Alkylidene phthalides and their derivatives have a rich chemistry and have received significant attention from the synthetic community. This is due to the diverse biological activities associated with the isobenzofuranone heterocyclic motif, which is present in natural products such as senkyunolide E and vermistatin. In addition, this framework has been exploited as a versatile building block in organic synthesis (Figure 1).[4]

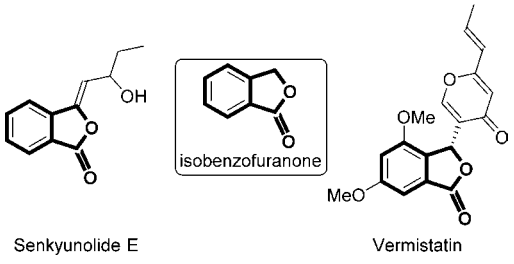
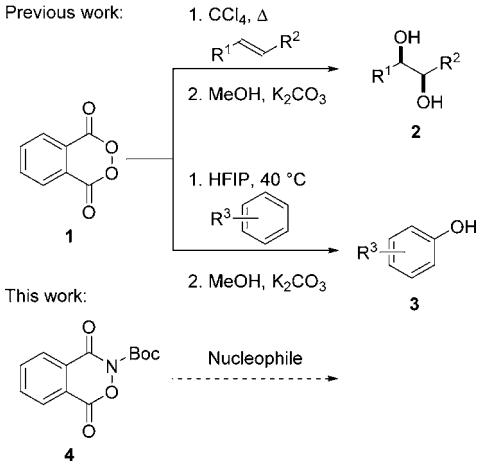


Figure 1. Isobenzofuranone skeleton.

Cyclic diacyl peroxides act as electrophilic oxidizing agents of electron-rich π-systems.[5,6] For example, phthaloyl peroxide **1** and its derivatives are effective in the *syn*-dihydroxylation of alkenes and the conversion of aromatic compounds to the corresponding phenols (Scheme 1). Phthaloyl peroxide **1** was first described as a monomer by Russell in 1955,[7] and its use in alkene oxidation was thoroughly investigated by Greene in a series of elegant studies.[5a−e] Despite this insightful work, exploitation of phthaloyl peroxide as an oxidant was not revisited until 2011 when Siegel and co-workers re-examined the use of **1** in alkene *syn*-dihydroxylation.[5g] A potential reason for the chemistry of **1** lying dormant for such a long period may well reside in the documented explosive nature of phthaloyl peroxide and the fact that this compound is reported to be very sensitive to shock.[5a] Since phthaloyl peroxides have been shown to be versatile compounds that have proved challenging to handle, we were intrigued to discover if their hydroxylamine counterparts would provide more stable reagents that were reactive with nucleophiles. In this paper, we describe the preparation of the *N*,*O*-diacylhydroxylamine derivative **4**[8] and show how reaction with enolate nucleophiles provides a simple stereoselective method for the preparation of alkylidene phthalides.

Scheme 1. Phthaloyl Peroxide as an Electrophilic Oxidant



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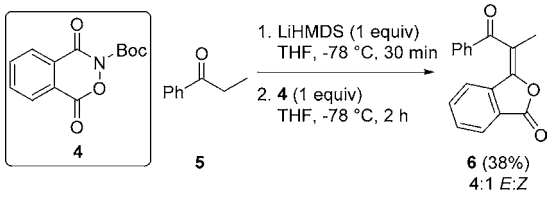
Our investigations began by treatment of commercial phthaloyl chloride with *N*-Boc-hydroxylamine in the presence of triethylamine to give **4** in 56% isolated yield after purification by trituration (see the Supporting Information for full details). In contrast to phthaloyl peroxide **1**, the hydroxylamine derivative **4** proved to be a bench-stable solid that was easy to manipulate and handle.

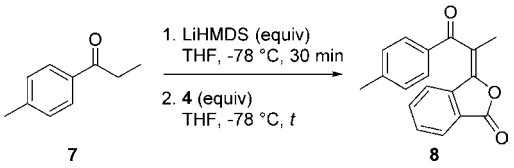
Having prepared **4**, we examined its reactivity with a series of nitrogen, sulfur, oxygen, and carbon nucleophiles. While **4** proved less reactive than malonoyl[6] and phthaloyl peroxides,[5] it provided an intriguing reactivity with lithium enolates. Treatment of propiophenone **5** with 1 equiv of lithium hexamethyldisilazide at −78 °C for 30 min followed by addition of a THF solution of **4** and allowing the mixture to react at −78 °C for a further 2 h led to the alkylidene phthalide **6** as a 4:1 mixture of diastereoisomers, the major isomer of which was isolated in 38% yield after chromatography (Scheme 2). This represented a novel

Scheme 2. Preparation of Alkylidene Phthalide



and selective method for the preparation of this class of heterocycle which has been prepared previously by methods including the photolysis of epoxybenzoquinones,[9] Wittig reaction of stabilized phosphonium ylides,[10] carbonylative palladium-catalyzed coupling of Baylis−Hillman adducts,[11] and the photolysis of tricarbonyl species.[12,13] Intrigued by the dense functionality introduced through this simple procedure together with the biological significance of the core structure prepared, we elected to investigate this reaction further. Selected data from the optimization of this process are collected in Table 1.

Table 1. Reaction Optimization



entry	LiHMDS (equiv)	**4** (equiv)	time (h)	conv[a] (%)	*E*/*Z*[a]
1	1.0	1.0	1	30 (23)	5:1
2	2.0	1.0	1	79 (62)	6:1
3	3.0	1.0	1	52	5:1
4[b]	2.0	1.0	1	45	4.5:1
5	2.0	1.0	5	54	6:1
6	**2.0**	**2.0**	1	**100 (83)**	**6:1**

[a]Determined by ^{1}H NMR spectroscopy on crude reaction mixture; isolated yield of major isomer shown in parentheses; [b]Reaction warmed to room temperature before stirring for **1** h.

Reaction of the lithium enolate derived from 4′-methylpropiophenone **7** with **4** (1 equiv) led to the product **8** (23% isolated yield) as a 5:1 mixture of diastereoisomers (Table 1, entry 1). Increasing the amount of base present to 2 equiv improved the amount of product significantly (Table 1, entry 2; 62% yield, 6:1 selectivity). Use of 3 equiv of base had a detrimental effect on the reaction outcome, delivering the product in just 52% conversion (Table 1, entry 3). Allowing the reaction mixture to warm to room temperature after addition of the electrophile (Table 1, entry 4) or extending the reaction time to 5 h (Table 1, entry 5) had no substantial effect on the reaction outcome. Addition of 2 equiv of both base and **4** resulted in complete consumption of starting material, an excellent yield, and high levels of stereoselectivity (Table 1, entry 6; 83% yield, 6:1 *E*/*Z*).

A potential mechanistic course for the transformation is outlined in Figure 2. The lithio-enolate **9** derived from

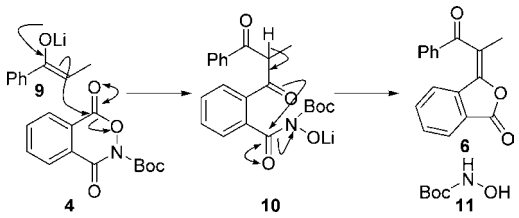


Figure 2. Potential mechanistic course for the formation of **6**.

propiophenone could add to either carbonyl group of **4**. Reaction with the O-substituted carbonyl group would lead to **10**, which could then deprotonate under the basic reaction conditions and ring close to give the observed product **6**. In support of this proposal, reaction of **5** under the optimized conditions gave *N*-Boc-hydroxylamine **11** in 70% isolated yield. The alternative bis-electrophiles phthalic anhydride and phthaloyl chloride were examined under the optimized reaction conditions (1.0 equiv **7**, 2.0 equiv LiHMDS, 2 equiv electrophile, −78 °C, 1 h). In each case, no clear indication for the presence of the alkylidene phthalide product **8** was observed by ^{1}H NMR spectroscopy of the crude reaction mixture, suggesting the reactivity observed was exclusive to the phthaloyl hydroxylamine derivative **4**.

Having developed a set of optimized conditions for the reaction of 4′-methylpropiophenone, we went on to examine a series of alternative substrates within the transformation (Figure 3). Reaction of 4′-, 3′-, and 2′-methylpropiophenone led selectively to the *E*-products **8**, **12**, and **13** in good to excellent yield (Figure 3, entries 1−3). Along with propiophenone (Figure 3, entry 4; 76%), it also proved possible to successfully introduce both activating (Figure 3, entry 5; 56%) and deactivating (Figure 3, entry 6; 41%) groups onto the aromatic ring of the nucleophile. Alternative substitution at the α-position of the ketone was also tolerated. Benzoin led to the *E*-product **16** with the same sense of selectivity as the propiophenone derivatives (Figure 3, entry 7; 39%). While butyrophenone gave the *E*-product **17** in an acceptable yield (Figure 3, entry 8; 40%), branching of the ketone at the β-position was less well tolerated (Figure 3, entry 9; 19%). Using 3-pentanone, it was found that the stereochemical outcome of the transformation could be manipulated simply by changing the polarity of the reaction medium (Figure 3, entries 10−12). Using THF as the solvent delivered the *Z*-isomer **19** selectively (*E*:*Z* 1:6; isolated yield of the *Z*-isomer 44%), whereas using HMPA as a cosolvent delivered both products in a 1:1 ratio, the *Z*-isomer being isolated in 43% yield (Figure 3, entry 11). Use of toluene as the reaction medium again provided the *Z*-isomer selectively, but the transformation was significantly less efficient than under the optimized conditions (Figure 3, entry 12; 28% yield). Cyclic ketones also proved to be effective substrates within the transformation, with cyclohexanone delivering the *E*-product in

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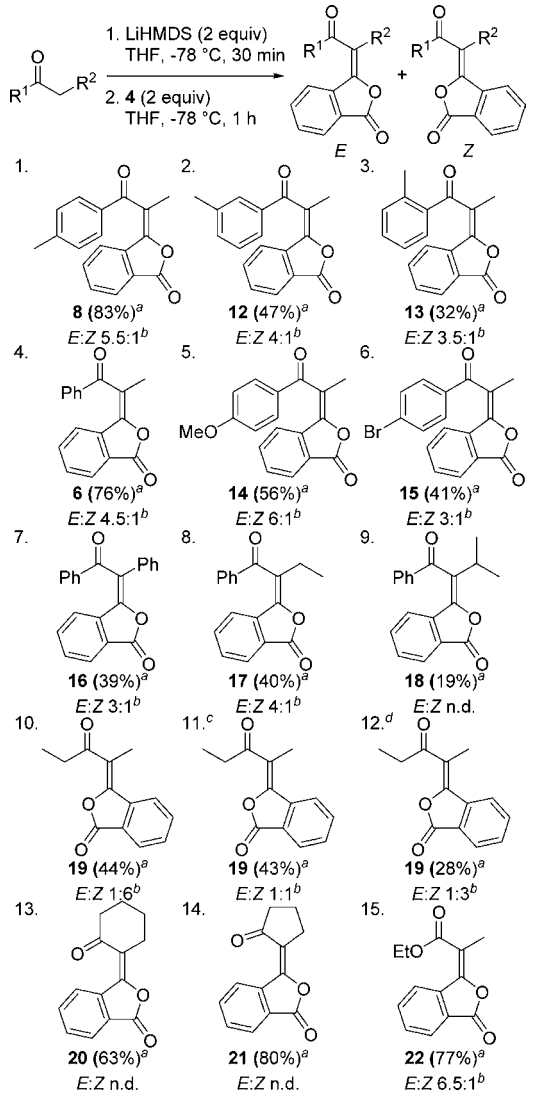


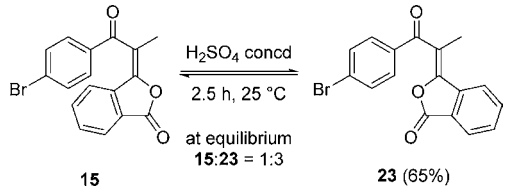
Figure 3. Substrate scope. (a) Isolated yield of major isomer. (b) Ratio determined by 400 MHz ^{1}H NMR spectroscopy of crude reaction mixture in $CDCl_3$. (c) 23% v/v HMPA used as solvent. (d) Toluene used as solvent.

63% isolated yield (Figure 3, entry 13) and cyclopentanone delivering the product **21** in an excellent 80% isolated yield (Figure 3, entry 14). We were unable to unequivocally determine the selectivity of these transformations by examination of the crude reaction mixture by ^{1}H NMR spectroscopy; however, the major isomer could be isolated from both of these transformations in 63% and 80% yield, respectively, after purification by SiO_2 column chromatography. Esters also proved to be effective substrates, with ethyl propionate delivering the *E*-product **22** with excellent 6.5:1 selectivity and 77% isolated yield for the major *E*-isomer (Figure 3, entry 15). Interestingly, under the optimized conditions, acetophenone gave the product of an aldol reaction in 93% yield.[14]

Assignment of the relative stereochemistry of adducts prepared was based upon comparison of analytical data to reported literature values.[10−13] Unequivocal reinforcement of these assignments came from X-ray crystallographic analysis of **8**, **15**, **19**, **21**, and **23** (see the Supporting Information for full details).

Stirring the *E*-isomer **15** at 25 °C in neat sulfuric acid for 2.5 h led to isomerization of the double bond (*E*:*Z* 1:3), from which the thermodynamically more stable *Z*-isomer **23** could be isolated geometrically pure in 65% yield after purification by SiO_2 column chromatography (Scheme 3).[15] This provides rapid and

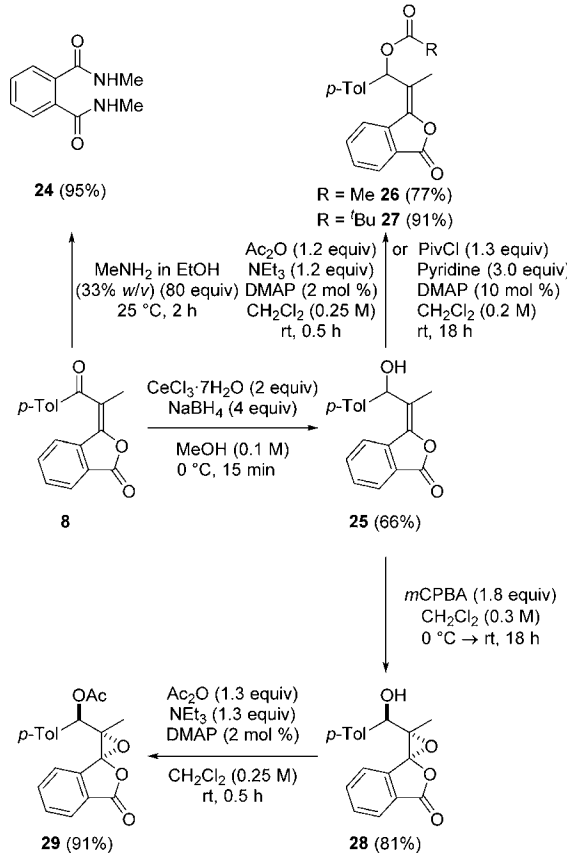
Scheme 3. Isomerization of Alkylidene Benzofuranones



convenient access to both isomeric forms of the alkylidene phthalide products. Resubmission of geometrically pure **23** to the isomerization conditions (H_2SO_4, 2.5 h, 25 °C) led to a thermodynamic 1:3 mixture of **15** and **23**, showing this isomerization is a fully reversible process.

A series of further transformations of the alkylidene phthalides was explored (Scheme 4). Treatment of **8** with methylamine

Scheme 4. Further Transformations of Alkylidene Phthalides



resulted in cleavage of the newly formed C═C to give dimethylphthalamide **24** in 95% yield. Selective reduction of the ketone group was achieved by reaction of **8** under Luche conditions[16] to give the alcohol **25** in 66% isolated yield without compromise in the stereochemical integrity of the double bond. O-Functionalization of the newly formed alcohol could be achieved through reaction with both acid anhydrides and acid chlorides in excellent yields (**26** 77%; **27** 91%). Directed

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epoxidation of **25** with *m*-CPBA (1.8 equiv) gave **28** stereoselectively (81%),[17] the relative stereochemistry of which was confirmed by single-crystal X-ray crystallographic analysis of **29** (see the Supporting Information for full details). Overall, this series of transformations shows that each of the distinct functionalities within the core alkylidene phthalide product can be manipulated selectively, allowing for effective diversification of the products.

In summary, the reagent **4** can be prepared in a single step by reaction of phthaloyl chloride with *N*-Boc-hydroxylamine **11** under basic reaction conditions. Treatment of enolates derived from cyclic or acyclic ketones as well as esters with 2 equiv of **4** leads to an alkylidene phthalide product stereoselectivity. The selectivity observed in the transformation can be altered by changing the polarity of the reaction medium. Isomerization of the products also proved possible under acidic conditions providing a convenient method by which to prepare this important class of heterocycle. The ability to manipulate the functional groups in the product suggests that this transformation will be applicable to the preparation of 3-substituted phthalides which are prevalent in many naturally occurring and biologically significant molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01203.

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

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Notes

The authors declare no competing financial interest.

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