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Modified Julia Olefination on Anhydrides: Extension and Limitations. Application to the Synthesis of Maculalactone B

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Supporting Information

ABSTRACT: The preparation of *exo*-enol esters from cyclic anhydrides is reported using a modified Julia olefination. The reaction is highly stereoselective. The Smiles rearrangement can be performed in a one-pot process, giving a straightforward access to *exo*-enol lactones. Furthermore, the reaction was extended to semistabilized sulfones, and this methodology was applied to the synthesis of maculalactone B.

exo-Enol esters are esters having an exocyclic carbon−carbon double bond at the α position to the oxygen. Benzalphthalides, *exo*-enol lactones structurally related to phthalic anhydride, have shown anxiolytic effects.[1] More recently, some *exo*-enol ester butenolides have been identified as antioxidants.[2] Many natural products contain these structures such as freelingyne[3] extracted from *Eremophila freelingii*, the antibiotic tetrenolin[4] isolated from *Micropolyspora*, some tetronic acids[5] from sponges, and natural alkylidene phthalides[6] extracted from celery (Figure 1). Halo-enol lactones are also structurally similar and could act as inhibitors of α-chymotrypsin.[7] *exo*-Enol esters can also be used as key intermediates in total synthesis.[8]

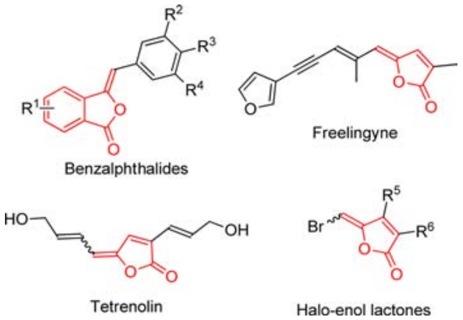
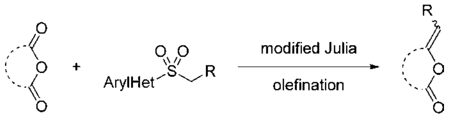


Figure 1. Natural products or biologically active compounds containing *exo*-enol esters.

Many methods have been developed to obtain *exo*-enol esters from anhydrides, such as Wittig reactions[9] or Gabriel[10] and Knoevenagel[11] type condensations, but they are limited to stabilized nucleophiles. The use of Grignard,[12] organolithium,[13] or Tebbe[14] reagents provides access to alkyl *exo*-enol esters, but only for the introduction of simple alkyl chains.

Our goal has been to extend the modified Julia reaction to unsaturated and saturated cyclic anhydrides and a variety of heteroaryl sulfones in order to show the functional group tolerance of our method and allow access to many butenolides and *exo*-enol esters inaccessible by other methods (Scheme 1).

Scheme 1. Modified Julia Olefination on Anhydrides



Initially developed on aldehydes and ketones,[15] the modified Julia reaction has been extended to carboxylic acid derivatives such as lactones, Boc-protected lactams, and imides by our group, providing access to di-, tri-, and tetrasubstitued *exo*-glycals,[16] mono- and difluoro *exo*-glycals,[17] *exo*-enamides,[18] and bicyclic lactam enamides.[19]

We first started our study by finding the optimal conditions for this reaction. We chose the commercially available, UV-vis phthalic anhydride **1** as the initial substrate. The *n*-propylphenyltetrazolyl sulfone **2** was prepared from inexpensive and odorless mercaptophenyltetrazole through a two-step process involving *S*-alkylation and *S*-oxidation.

Our previous studies on the modified Julia reaction have shown that the addition of sulfone to the carbonyl derivative should generally be performed at −78 °C in THF in the presence of an excess of $BF_3{\cdot}Et_2O$ and LiHMDS (2 equiv). These conditions were applied to phthalic anhydride and *n*-

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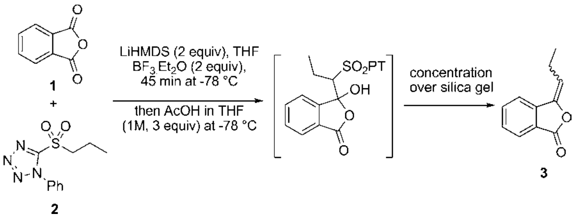
propylphenyltetrazolylsulfone by varying the number of equivalents of each reagent (Table 1).

Table 1. Optimization



entry	anhydride (equiv)	sulfone (equiv)	$BF_3{\cdot}Et_2O$ (equiv)	LiHMDS (equiv)	yield (%)
1	2	1	2	2	90
2	1.2	1	2	2	85
3	1	1	2	2	83
4	1	1.2	2	2	78
5	1	1.5	2	2	71
6	1.2	1	0	2	64
7	1.2	1	2	1	7

In the initial procedure,[16] the second step (Smiles rearrangement and elimination) was performed with 3 equiv of DBU. This procedure only gave traces of product in this case. So, instead of using DBU for the elimination step, we found that the Smiles rearrangement could occur by concentration over silica gel following treatment with acetic acid in a one-pot process. Thereby, we avoid an aqueous treatment and the second step using this procedure.

We found that an excess of anhydride gave better yields, while an excess of sulfone lowering the yields and leading to difficult purifications (see entries 1 and 2 vs 4 and 5, Table 1).

We next tried to vary experimental conditions such as the presence of the activating agent ($BF_3{\cdot}Et_2O$) or number of equivalents of LiHMDS, but no improvement of yield was observed (entries 6 and 7, Table 1). The carbonyl groups of an anhydride are expected to be electrophilic enough to permit the addition of a lithiated sulfone, yet the presence of an activating agent such as $BF_3{\cdot}Et_2O$ gives better yields (entry 2 vs 6, Table 1). An excess of LiHMDS is necessary during the addition step (entry 2 vs 7).

Although the 1:1 anhydride/sulfone ratio gave a good yield, we chose the conditions of entry 2 for the rest of the study in order to get better yields. Under these conditions, we obtain a partially separable 90:10 (*E*/*Z*) mixture of phthalide **3**. The isomers have been characterized by NOE experiments (Figure 2).

It is known that the nature of the heteroaromatic moiety in the modified Julia reaction can modify the *E*/*Z* selectivity. We therefore prepared four sulfones with different heteroaryl groups from the corresponding mercapto−heteroaromatic compounds following the same procedures described above. The study of the stereoselectivity according to the nature of the heteroaromatic group is described in Table 2.

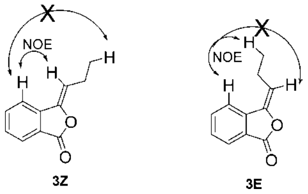
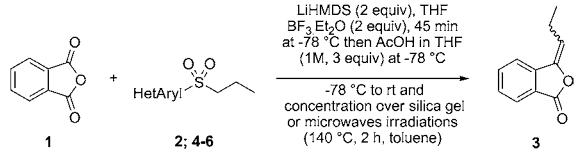
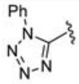
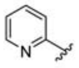
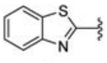
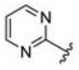


Figure 2. NOE effect on compound **3Z** and **3*E***.

Table 2. Influence of the Heterocycle on the Stereoselectivity



entry	hetaryl	yield (*E*/*Z*) [%]	entry	hetaryl	yield (*E*/*Z*) [%]
1	 **2**	85 (90:10)	3	 **5**	40[a] (75:25)
2	 **4**	70 (60:40)	4	 **6**	52 (75:25)

[a] Second step: microwaves (toluene, 2 h, 140 °C).

No inversion of selectivity was observed, and we only saw a decrease of the *E*/*Z* ratio and the yield in all cases compared to entry 1. The elimination step over silica gel is more difficult in the case of benzothiazolylsulfone **4** (entry 2) and requires heating of the solution before concentration. In the case of the pyridinyl sulfone (entry 3), the second step was performed under microwave irradiation according to our previous studies.[17c]

Then we extended this reaction to a range of sulfones to show the chemical functional group tolerance of our modified Julia procedure. Using the procedure described above, we prepared sulfones bearing functionalized groups on the R chain such as terminal alkene, nitrile, amine, and different ethers. These sulfones were engaged in modified Julia reactions to give the phthalide derivatives from phthalic anhydride (Scheme 2).

Alkyl phthalides **3**, **7**, and **11** were obtained in good yields. Sulfones bearing the terminal alkene also give the corresponding compound **8** in high yield. The methylene compound **9** was obtained in small quantities, as purification by chromatography seems to be a problem in that case. Using sulfones bearing a protected alcohol, the desired product was isolated in good yields (compounds **12** and **14**) except for compound **13**, which is difficult to purify. The cyclopropyl phthalide **10** was obtained from the bromo sulfone through a multistep process via the cyclopropyl sulfone formed in situ. For compound **16**, the poor yield could be explained by the presence of the cyano group which can act as an electrophile during the addition step. The product **15** containing a morpholine moiety was isolated in good yield. Lastly, we studied the specific situation of the semistabilized sulfone **18** (Scheme 3). While no reactivity was previously observed between benzothiazolyl-semistabilized sulfones and lactones, we were surprised to observe the formation of the compound **17** in moderate yield as the *E* isomer. In order to increase the yield and modify the selectivity, we concentrated our efforts on the use of pyridinyl sulfones. Thus, we recently showed that in the particular case of less reactive sulfone such as α-difluorinated sulfone the use of the pyridinyl moiety was necessary.[17c] This observation was confirmed by our results. From sulfone **19**, compound **17** was prepared in 43% yield with the *Z* isomer as the major product (3/7 *E*/*Z* mixture).

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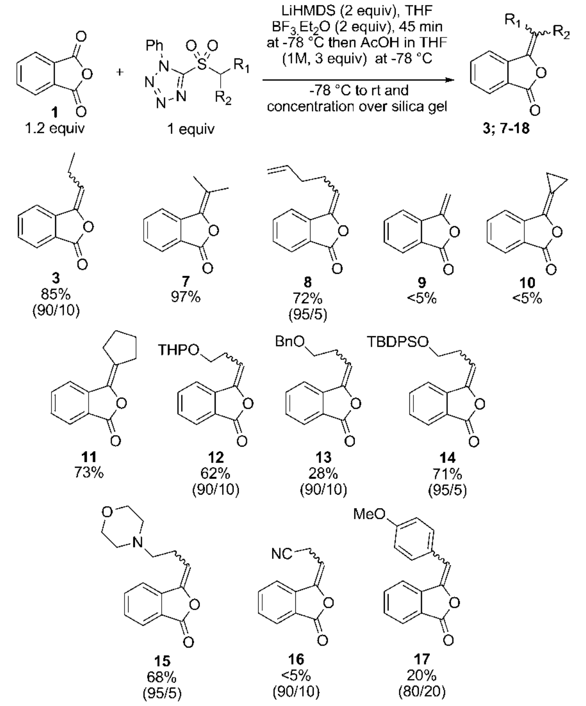
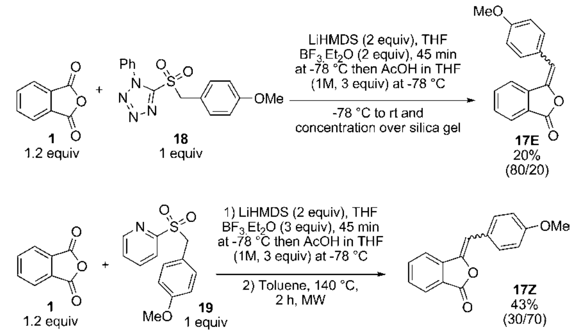
Scheme 2. Scope of the Sulfones

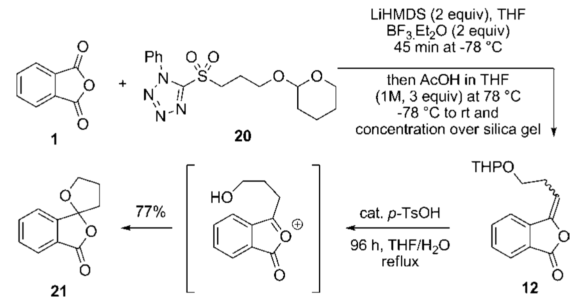


Scheme 3. Extension to Semistabilized Sulfones



The reaction between tetrahydropyran (THP)−ether−sulfone **20** and phthalic anhydride gave the corresponding phthalide **12**. A catalytic amount of *p*-toluenesulfonic acid allows the in situ deprotection of the THP and the intramolecular cyclization of the resulting primary alcohol on the oxonium intermediate to form the spiroketal **21** in 77% yield. By comparison with other spiroketalization on *exo*-glycals,[20] this cyclization is more difficult, requiring heating at reflux of the THF/H_2O mixture over 4 days (Scheme 4).

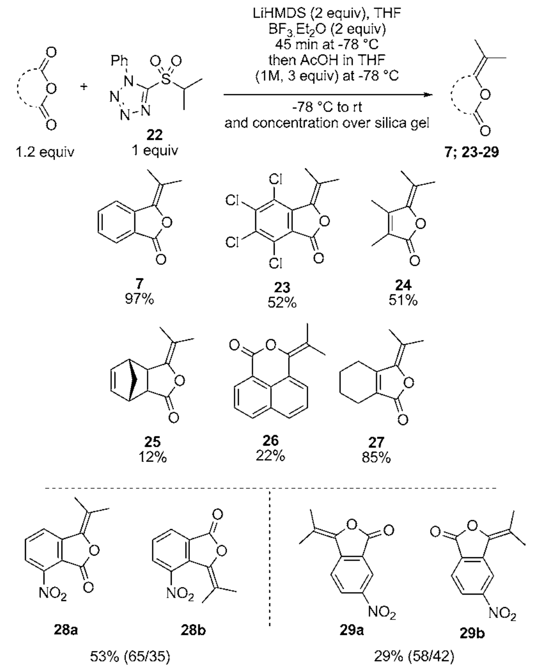
Scheme 4. Formation of a Spiroketal Derivative



At room temperature in dichloromethane, compound **12** leads to traces of product **21** (8%). Starting material **12** and the THP-deprotected compound (32%) are recovered after the reaction.

We then chose the isopropyl sulfone **22** to evaluate the scope of the reaction with anhydrides and to avoid potential *E*/*Z* isomers. The results are presented in Scheme 5.

Scheme 5. Scope of Anhydrides



The desired products **7**, **23**, **24**, and **27** were obtained in good yields from the corresponding anhydrides. The olefination of the norbornene anhydride was performed with a 12% yield (compound **25**). This result shows that the reaction works with a saturated anhydride, which is a less favorable case. This preliminary result is encouraging, and further studies could extend the reaction to additional saturated anhydrides. Concerning the limit of the methodology, the reaction on maleic, succinic, and glutaric anhydride did not give the desired product, probably due to the potential Michael addition or the presence of acidic protons on the substrate.

In order to evaluate the regioselectivity of the reaction, the modified Julia olefination was performed on 3- and 4-nitrophthalic anhydride. In both cases, the sulfone reacted preferentially on the less hindered carbonyl group. Thus, the reaction seems to be more sensitive to steric hindrance than to electronic effects.

We then turned our attention to the application of our methodology to the synthesis of maculalactone B.[21] This natural compound was isolated from marine cyanobacterium *Kyrtuthrix maculans* and belongs to a larger family of derivatives based on the tribenzylbutyrolactone skeleton, which inhibits the formation of biofilms in marine systems (Figure 3).[22]

Starting from commercially available dichloromaleic anhydride, radical substitution in toluene afforded dibenzyl maleic anhydride.[23] Then, the modified Julia olefination using pyridinyl benzyl sulfone provided maculalactone B in 63% yield. As shown previously in Scheme 3, the use of pyridinyl sulfone was necessary to obtain a good yield and a total *Z* selectivity

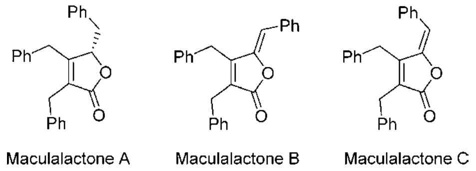
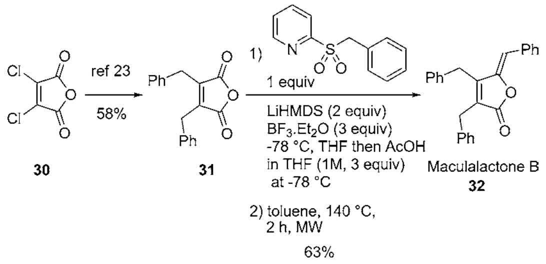


Figure 3. Maculalactones A–C.

(Scheme 6). Thus, maculalactone B was obtained in two steps in 37% global yield. This route is more valuable compared to previous syntheses in terms of number of steps and global yield.[24]

Scheme 6. Two-Step Synthesis of Maculalactone B



We have extended the modified Julia reaction to anhydrides. The reaction has been optimized, and the procedure was modified to a one-pot process involving a Smiles rearrangement over silica gel. Alkyl and functionalized sulfones have been synthesized and used to obtain a wide variety of phthalide derivatives, showing the functional group tolerance of our method. Different anhydrides have also been used to obtain various structures and to extend the olefination to anhydrides other than those which can be found in the literature. Further studies will be done to increase the scope and obtain more diversity in order to show the general aspect of our method. Otherwise, this methodology was applied to the total synthesis of maculalactone B. We demonstrated that this pathway is short, efficient, and stereoselective.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02160.

Full experimental details, data for all new compounds, and ^1H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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