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From Carbamate to Chalcone: Consecutive Anionic Fries Rearrangement, Anionic Si → C Alkyl Rearrangement, and Claisen−Schmidt Condensation

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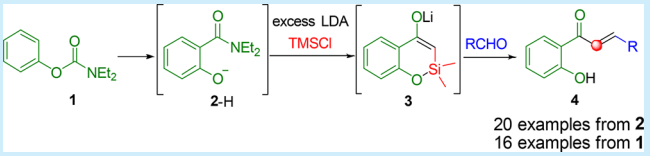
Supporting Information

ABSTRACT: A highly efficient one-pot procedure was developed for the synthesis of various 2′-hydroxychalcones from phenyl diethylcarbamate, featuring consecutive Snieckus−Fries rearrangement, anionic Si → C alkyl rearrangement, and Claisen−Schmidt condensation in a single operation. The applicability of this protocol was demonstrated by the highly efficient synthesis of the anti-inflammatory natural product lonchocarpin. The mechanism insight is also provided.



Chalcones, comprising a common 1,3-diphenyl propenone template, are precursors in the biosynthesis of flavonoids and isoflavonoids.[1] The word Chalcone is derived from the Greek word *Chalcos*, meaning bronze, and flavone is derived from the Latin word *flavus*, meaning yellow. Chalcones, flavonoids, and aurones (Figure 1) are composed of pigments,

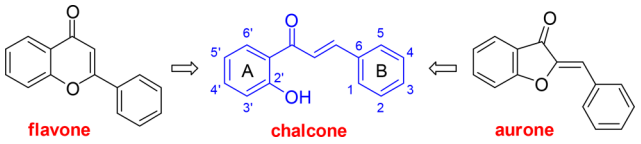


Figure 1. Chalcone as a precursor in the biosynthesis of flavonoids.

of which the color changes from orange to yellow in some plants. As a primary subgroup of the flavonoid family, naturally occurring chalcones and their synthetic analogues possess a wide range of biological activities, including antiviral and anticancer,[1b,2] antibacterial,[3] anti-inflammatory,[2b,d,3a,4] antimicrobial,[5] antiulcer and spasmolytic,[6] antiproliferative,[7] anti-HIV,[8] antioxidant,[2d,3a,9] analgesic,[1b,3a] and immune-modulator properties.[10] Natural chalcones also exist as various types of dimers, oligomers, Diels−Alder adducts, and conjugates,[11] which are primarily attached with hydroxyl and methoxy functionalities, particularly in the 2′ position.[9] More importantly, the presence of the α,β-unsaturated ketone moiety was found to be responsible for the observed versatile biological activities.[12] Clinical studies have proven the excellent bioavailability of chalcones and their maximum tolerance in the human body.[13] Thus, chalcones have become a focus of continued interest among both academic and industrial researchers. Several synthetic routes have been reported for the synthesis of chalcones, generally involving a Claisen−Schmidt condensation under homogeneous conditions in the presence of acid or base.[14] Herein, we report an easy preparation of 2′-hydroxychalcones from aryl carbamates in a highly efficient one-pot manner.

The expanded use of silicon reagents in organic synthesis, resulting from their low cost, versatile properties, and application to a wide range of reactions, has greatly increased the prominence of organosilicon chemistry.[15] In a previous study, we reported the formation of ortho-Fries hydroxyketones from aryl diethylcarbamate through consecutive Snieckus−Fries[16] and Si → C alkyl rearrangements (Scheme 1).[17]

Mechanistic studies showed that this transformation featured a complex-induced proximity effect (CIPE)[18] in the deprotonation of the silyl ether intermediate, followed by an intramolecular nucleophilic addition for the formation of oxasilinolate **3** and the fission of **3** to *ortho*-Fries hydroxyketone **5** upon an aqueous workup. Based on these findings, we raised the following question: if oxasilinolate **3** is the key intermediate instead of a hypervalent silicon species, can we use **2** as an enolate source in a variety of reactions to expand the scope of this *ortho*-directed acylation methodology? In the

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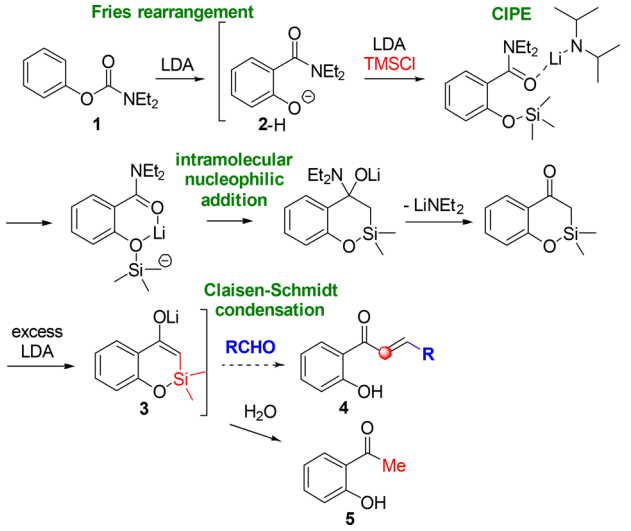
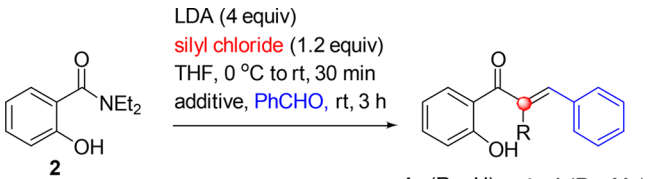
Scheme 1. Concise Synthesis of *ortho*-Fries Hydroxyketone and Chalcones from Phenyl Carbamate



present study, we first examined the use of lithium enolate ion **3** as an effective nucleophile in aldol and Claisen−Schmidt condensations to develop a new and capable method to synthesize chalcone derivatives **4** from aryl carbamate **1**.

To simplify this investigation, lithium enolate ion **3** was first generated from *ortho*-Fries hydroxyamide **2** by treatment with 4 equiv of lithium diisopropylamide (LDA) and 1.2 equiv of trimethylsilyl chloride (TMSCl) in tetrahydrofuran (THF) at 0 °C. After 30 min at room temperature, the reaction mixture containing lithium enolate ion **3** was trapped by the addition of benzaldehyde. To our delight, chalcone **4a** was isolated in 38% yield (Table 1, entry 1), along with 2-hydroxyacetophenone,

Table 1. Optimization of the Reaction Conditions



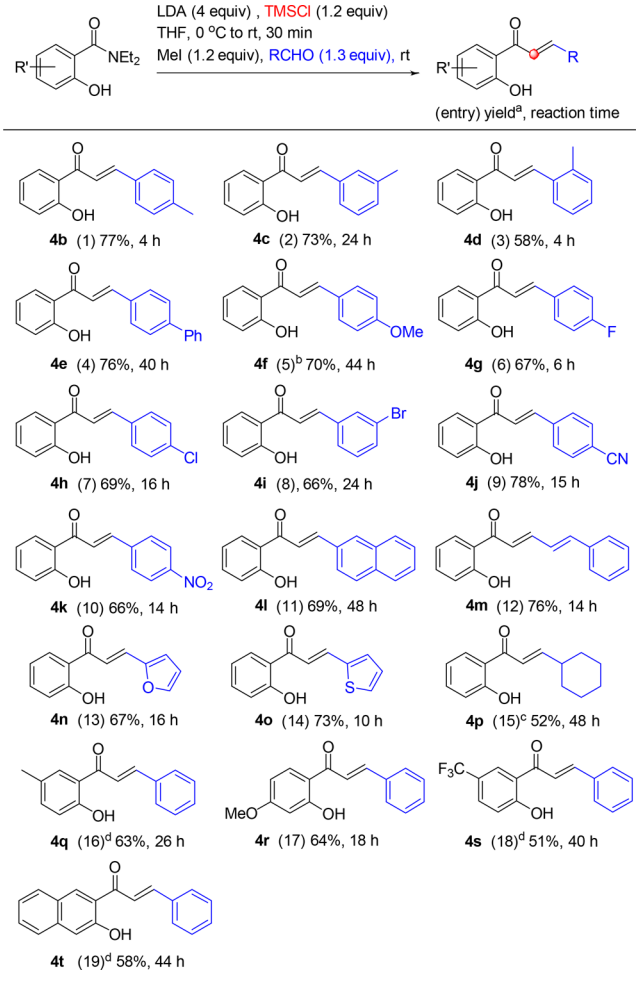
entry	silyl chloride	PhCHO (equiv)	additive (equiv)	yield (%)[a]
1	TMSCl	1.3	-	38
2	TMSCl	2.0	-	65
3	TMSCl	1.3	MeI (1.2)	77
4	$Ph_2MeSiCl$	1.3	MeI (1.2)	65
5	Et_3SiCl	1.6	MeI (1.2)	73 (97:3)[b,c]
6	Pr_3SiCl	2.6	MeI (1.2)	36 (90:10)[b,c]
7	Bu_3SiCl	2.6	MeI (1.2)	55 (93:7)[b,c]

[a]Isolated yield. [b]Ratio of *E*/*Z* isomers. [c]40 h reaction time.

N,*N*-diethylbenzamide, and benzyl alcohol. Apparently, lithium diethylamide was produced from an intramolecular nucleophilic addition of the α-silyl carbanion, followed by reaction with benzaldehyde through a Cannizzaro-type reaction to give the disproportionation products, phenyl diethylamide and benzyl alcohol.[19] Unreacted **3** was degraded to 2-hydroxyacetophenone (**5**) after an aqueous workup, which deteriorated the yield of the chalcone product. Based on the above reactivity, 2 equiv of benzaldehyde was used in entry 2 to improve the yield of **4a** to 65%. To reduce the unnecessary consumption of benzaldehyde, MeI was added into the reaction to trap the lithium diethylamide, further improving the yield of this optimized reaction condition to 77% (entry 3). When diphenylmethylsilyl chloride was used as the alkyl source, the two larger phenyl groups hindered the condensation step, decreasing the yield of **4a** to 65% (entry 4). Interestingly, 1,3-diphenyl-2-methyl propenone (**4a-1**) in a predominant *E* form was prepared in good yield using triethylsilyl chloride in the same method (entry 5). Other chlorosilanes such as tripropylsilyl chloride (entry 6) and tribuylsilyl chloride (enrty 7) were also subjected to the same conditions to construct the trisubstituted olefins **4a-2** and **4a-3** in 36% and 55% yield.

We next explored the substrate scope of the aldehyde and hydroxyamide in this transformation. As shown in Table 2,

Table 2. Scope of Aldehyde and Hydroxyamide



[a]Isolated yield. [b]Aldehyde was added at 0 °C, and the reaction was kept at rt. [c]2.6 equiv of aldehyde was used, and the reaction was kept at 50 °C. [d]Reaction was kept at 45 °C.

benzaldehydes bearing electron-donating (entries 1, 2, 4, 5) and electron-withdrawing (entries 6−10) functional groups in the para or meta position were all tolerated in the reaction at 35 °C, with the corresponding chalcones (**4b**, **4c**, **4e**−**4k**) isolated in 66−78% yields. The reaction with bulkier *ortho*-toluylaldehyde (entry 3), which could interfere with the nucleophilic addition, afforded **4d** in slightly lower yield

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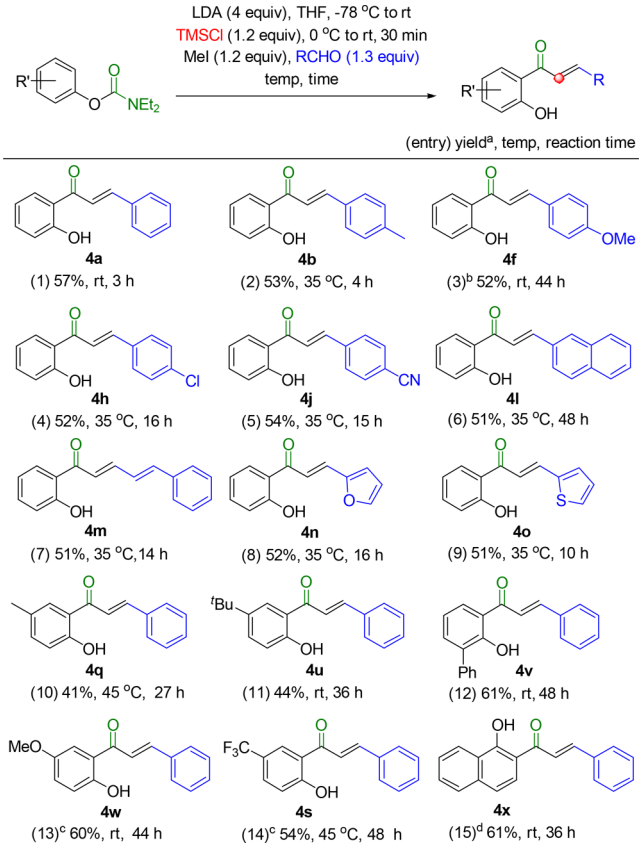
(58%). In addition to substituted benzaldehydes, 2-naphthaldehyde (entry 11), cinnamaldehyde (entry 12), and heteroaryl aldehydes (entries 13 and 14) also underwent this one-pot transformation in 67−76% yields. The reaction with cyclohexyl aldehyde (entry 15) at a higher reaction temperature (50 °C) with an increased amount of each employed aldehyde (2.6 equiv) smoothly gave product **4p** in 52% yield after 48 h. Finally, hydroxyamides bearing electron-donating groups (Me, OMe), an electron-withdrawing group (CF_3), and naphthalene were tested, and the corresponding chalcone products (**4q**−**4t**) were isolated in 51−64% yields (entries 16−19).

After the successful synthesis of chalcones from *N*,*N*-diethyl-2-hydroxybenzamide through the Claisen−Schmidt condensation between oxasilinolate **3** and aldehydes, we next examined the feasibility of implanting an anionic Fries rearrangement into the one-pot protocol. Gratifyingly, the *ortho*-lithiated phenyl diethylcarbamate [**1**-H] underwent a facile intramolecular [1,3]-acyl migration to afford *o*-carbamoyl phenolate [**2**-H] at room temperature, which was subsequently quenched with TMSCl at 0 °C and benzaldehyde at room temperature in the presence of MeI to furnish chalcone **4a** in a one-pot procedure with 57% yield (Table 3, entry 1). Likewise, the employment of various benzaldehydes readily provided B-ring substituted chalcones **4b**, **4f**, **4h**, and **4j** in similar yields (entries 2−5). The use of 2-naphthaldehyde (entry 6) and cinnamaldehyde (entry 7) gave adducts **4l** and **4m** in 51% yields. Reactions with 2-furaldehyde and 2-thenaldehyde afforded **4n** and **4o** in 52% and 51% yields, respectively (entries 8 and 9). Finally, a series of substituted phenyl diethylcarbamates were tested in this method. *para*-Tolyl, *para*-(*tert*-butyl)phenyl, and *ortho*-phenyl phenyl diethylcarbamates were transferred to chalcones **4q**, **4u**, and **4v** smoothly in 41−61% yields. Lithium tetramethylpiperidide and TBDMSCl were used instead of LDA and TMSCl to promote the efficiency of the Fries rearrangement of *para*-methoxy and *para*-trifluoromethyl phenyl diethylcarbamates, and **4w** and **4s** were obtained in 60% and 54% yields, respectively (entries 13 and 14). Interestingly, when naphthyl diethylcarbamate was submitted to the standard reaction conditions, methylation on oxasilinolate **3** happened as a side reaction. The resulting ethyl ketone and the desired chalcone **4x** were formed in a 1:3 ratio in 50% yield. The yield of **4x** was further improved to 61% by using a greater amount of benzaldehyde instead of adding MeI (entry 15).

With the success of the one-pot protocol lending credibility to intermediate **3** and our proposed mechanism, we were also interested in further mechanism studies based on our previous report. The failures in isolating oxasilinone led us to replace the hydroxyl with an amine and use bulkier groups to protect the silicon atom. To our delight, in the case of the analogous *ortho*-(methylamino)amide the corresponding azasilinanone was isolated in 84% yield after treatment with 4 equiv of LDA and 2.5 equiv of *tert*-butyldimethylsilyl chloride (TBDMSCl) in THF at 0 °C.[20] The 5-bromo derivative similarly gave the azasilinanone **6** in 67% yield. Recrystallization from chloroform yielded crystals suitable for X-ray diffraction (shown in Figure 2), providing further evidence supporting the mechanism we proposed in our previous report[17] as well as the existence of intermediate **3**.

Table 3. Syntheses of Various 2′-Hydroxychalcones from Aryl *N*,*N*-Diethylcarbamates



[a]Isolated yield. [b]Aldehyde was added at 0 °C, and the reaction was kept at rt. [c]Lithium tetramethylpiperidide and TBDMSCl were used instead of LDA and TMSCl. [d]RCHO (2 equiv) without MeI.

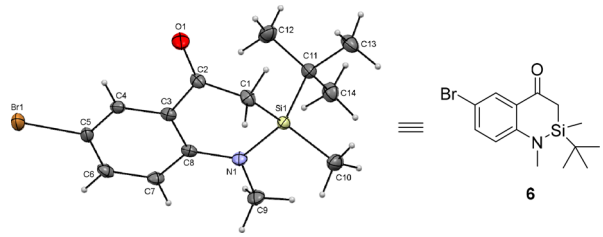


Figure 2. Molecular structure of **6**. Thermal ellipsoids are set at 50% probability level. Selected bond distances (Å) and angles (deg): N1−Si1 1.746, C1−Si1 1.859, N1−Si1−C1 101.29, O−C2−C3−C4 21.94.

The applicability of this one-pot transformation was demonstrated by a concise and protecting-group-free synthesis of lonchocarpin, a natural product that possesses numerous pharmacological properties such as anti-inflammatory,[21] antioedematogenic,[22] antibacterial,[23] and gastroprotective effect by inhibiting H^+, K^+ ATPase activity[24] and inhibition of nitric oxide production in lipopolysaccharide-stimulated BV2 microglial cells.[25] As shown in Scheme 2, 2,2-dimethyl-2*H*-chromen-5-ol **7** prepared from senecio aldehyde and 1,3-cyclohexanedione through a reported two-step procedure[26] was transferred to carbamate **8** in 89% yield. Carbamate **8** was then subjected to the one-pot protocol under standard reaction conditions to furnish natural product lonchocarpin **9** in 62% yield.[27]

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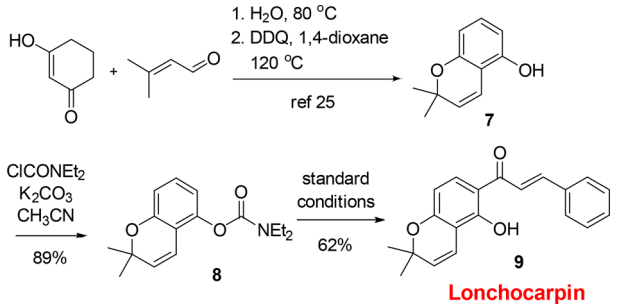
Scheme 2. Concise Synthesis of Lonchocarpin



In this study, a highly efficient one-pot procedure was developed for the syntheses of various 2′-hydroxychalcones bearing different substituents in the A- and B-rings. The concise synthesis of the anti-inflammatory agent lonchocarpin further demonstrated the utility of this transformation, which featured consecutive Snieckus−Fries rearrangement, anionic Si → C alkyl rearrangement, and Claisen−Schmidt condensation in a single procedure. This new advancement serves as an extension of the *ortho*-directed alkylation that will greatly benefit the research of chalcones in the fields of natural product synthesis and natural product, agriculture, food, and pharmaceutical chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02269.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 1564702 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Professor E. J. Corey in celebration of his 90th birthday.

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Information) in 20% yield along with azasilinanone as the major product because of the bulky *tert*-butyl group on the side.
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