Advances in the methodology of a multicomponent synthesis of arylnaphthalene lactones†

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Material and energy inefficiencies in total synthesis can arise from a lack of step economy. Multicomponent syntheses have the potential to optimize step economy and, in turn, to minimize not only waste, but also exposure to hazardous chemicals. Therefore, multicomponent syntheses are of immense interest to the field of Green Chemistry. Herein is described a multicomponent synthesis of arylnaphthalene lignan lactones, which are valuable natural products with promising anticancer and antiviral properties. In an effort to improve our previously reported one-pot, multicomponent synthesis an approach using phenylacetylene, phenylpropargyl chloride, carbon dioxide, catalytic silver iodide, and catalytic 18-crown-6 ether was developed. This methodology was then successfully applied to the preparation of dehydrodimethylconidendrin and its regioisomer, dehydrodimethylretroconidendrin.

Introduction

The achievements in the total synthesis of natural products are among the most important contributions of the field of organic chemistry. These achievements, however, have been a source of very high waste production as a result of material and energy inefficiencies and a lack of step–and atom–economy. It is estimated that ~80% of waste generated during a typical chemical transformation is due to use of solvent.[1] Therefore, in addition to the accumulation of losses due to incomplete conversion, sometimes referred to as the "arithmetic demon," multi-step syntheses have an inherent waste associated with solvent use at each step.[2] One way to minimize this inherent inefficiency is to perform as many transformations as is feasible in a single reaction vessel.

In an effort to illustrate how one such approach can begin to overcome some of the aforementioned limitations, the total synthesis of arylnaphthalene lactones was undertaken (Fig. 1). This class of compounds is an important class of pharmaceutical interest due to its antiviral and antitumor activities.[3-5] For this reason an efficient synthesis to access a broad range of arylnaphthalene lactones is highly desirable. Several synthetic methodologies have been developed in recent years to access both the arylnaphthalene core and more specific targets. Nevertheless, most rely on multi-step syntheses that are deficient in terms of Green Chemistry.[6-9]

Notably, there was a previous synthesis in 1991 by one of this paper's co-authors (PTA) that utilized the same core transformations and therefore serves as a useful comparison.[10] In this earlier work, hydrolysis of the propiolate ester was required to access the acid starting material, which was then converted to an acyl chloride. Reaction with a phenylpropargyl alcohol to generate the diyne ester was then undertaken before undergoing the thermal [2+2+2] cycloaddition in a separate step to generate the desired arylnaphthalene lactone. In total, this approach required four steps and used ethanol, dichloromethane (DCM) and xylenes as solvents. Our group recently attempted to resolve some of these shortcomings by developing a catalytic, multicomponent/cycloaddition reaction which incorporates the use of carbon dioxide as renewable feedstock. As hoped, this synthesis proved more efficient than the traditional multi-step syntheses in accessing the desired arylnaphthalene lactones.[11]

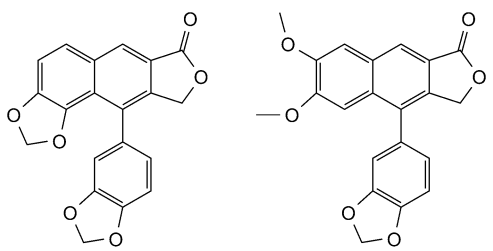

Fig. 1 Representative naturally occurring arylnaphthalene lactone lignans.

In an effort to complete this work, the preparation of known natural products and their closely related analogs was investigated; however the conditions reported earlier did not yield the desired products. The 3,4-methylenedioxyphenylpropargyl bromide reactant used for the original coupling appeared to be consumed by side reactions before any product could be generated. This outcome is believed to be related to the instability of electron-rich bromo-alkyne under the reaction conditions. With the intention of improving the previous synthesis for application to known natural products, we considered the use of alkyne

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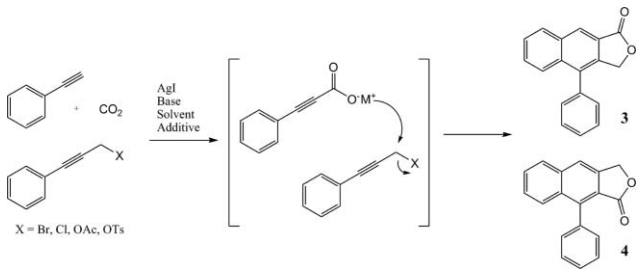
reagents bearing less reactive or more stable leaving groups such as acetate, tosylate, and chloride. Further, a full investigation of reaction parameters such as base, solvent, and phase transfer catalyst (PTC) selection was undertaken.

Results and discussion

In seeking new conditions to be applied to the synthesis of natural products and their closely related analogs, we first sought to modify the original arylnaphthalene lactone synthesis (Scheme 1). Replacing the bromide leaving group with an acetate group was first investigated but with no success, likely owing to the insufficient electrophilicity of the acetate group. Employment of a tosylate group was also attempted but required a stoichiometric amount of halogenated salt to be used. It was believed that in the presence of bromide salt, the tosylate could perhaps be displaced producing *in situ* phenylpropargyl bromide.

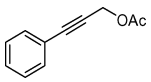
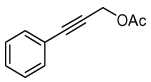
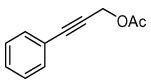
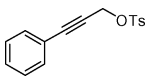
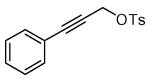
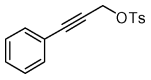
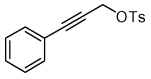
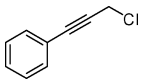
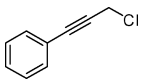
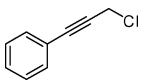
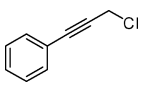
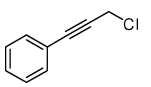
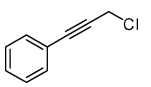
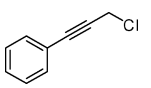
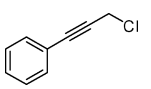
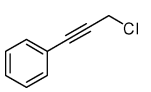


Scheme 1 General multicomponent approach to arylnaphthalene lactones.

Following a similar line of thinking, a catalytic amount of salt should be sufficient to drive the reaction since the halogen is not part of the final product. However, a catalytic amount of salt yielded only a small amount of product with a yield usually equal to or less than the amount of salt originally added. Both of these findings underscore once more the importance of the silver–halide interaction as a driving force for the desired coupling. Because the presence of a halogen group was apparently a necessity for the success of the first coupling step, we turned our attention to a chloride leaving group. Entries 8 to 16 in Table 1 present the results of this study. As expected, replacing the substrate phenylpropargyl bromide by phenylpropargyl chloride slowed the reaction rate and more than 20 h were needed to reach completion. Interestingly the use of a phase transfer catalyst such as tetrabutylammonium bromide or chloride significantly increased the reaction rate. This was usually accompanied by an increase of the carbonate byproduct, implying that the potassium carbonate base could be solubilized by the presence of the phase transfer catalyst. Following this observation, other phase transfer catalysts such as 18-crown-6 were tested.

The use of 18-crown-6 ether was the most effective and resulted in a decrease of the carbonate byproduct. In addition to being soluble in *N*,*N*-dimethylacetamide (DMA), 18-crown-6 ether is known to trap monovalent cations. As such, it is possible that the propiolic acid intermediate may exist in an ionic state, coordinated with the crown ether/cation complex.[12,13] Such a complex would likely increase the nucleophilicity of the intermediate and thus decrease byproduct formation.

Table 1 Leaving group and PTC screen

Entry[a]	Reagent	Additive	Time	Product 3	Product 4
1		—	6	—	—
2		KBr	6	—	—
3		TBP-Br	6	—	—
4		—	6	—	—
5		TBA-I	6	—	—
6		10% TBP-Br	6	Trace	Trace
7		60% TBP-Br	6	22	10
8		—	6	10	6
9		KBr	6	9	7
10		TBA-Br	6	23	15
11		TBA-Cl	6	28	22
12		TBA-I	6	26	17
13		TBP-Br	6	24	16
14		TBH-Br	6	28	19
15		18-Crown-6	6	30	20
16		18-Crown-6 3 A mol sieve	18	34	22

[a] All reactions were performed on a 0.5 mmol scale at 100 °C under 1 atm of CO_2 using 0.2 eq. of PTC or salt where indicated. All yields are isolated after chromatography. TBP = tetrabutylphosphonium, TBA = tetrabutylammonium, TBH = tributylhexadecylphosphonium.

Table 2 Solvent and base screen

Entry	Base	Solvent	Product 3	Product 4
1	K_2CO_3	BMIM-Br	Trace	Trace
2	K_2CO_3	Propylene carbonate	19.3	9.7
3	K_3PO_4	Propylene carbonate	Trace	Trace
4	K_2CO_3	NMP	—	—
5	t-BuOK	DMA	40.7	20.3
6	K_3PO_4	DMA	4.0	2.0
7	Hunig's base	DMA	—	—
8	DBU	DMA	—	—

All reactions were performed on a 0.5 mmol scale at 100 °C under 1 atm of CO_2 using 0.2 eq. of 18-crown-6 for 6 h. All yields were determined by ^{1}H NMR.

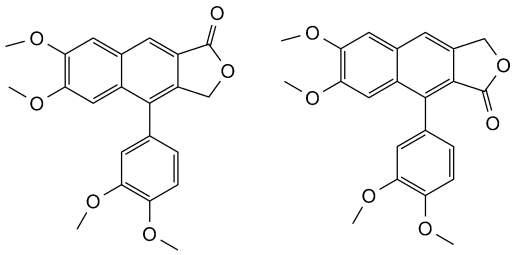
In an effort to further improve the reaction conditions, we monitored the effect of various bases and polar solvents on the yield of the reaction. Results are presented in Table 2.

Since ammonium salts proved to be quite effective in accelerating the rate of the reaction, it was envisioned that ammonium-based ionic liquids, which are polar solvents, could potentially be used as both solvent and catalyst.[14] DMA was therefore replaced by butylmethylimidazolium bromide (BMIM-Br) and butylmethylimidazolium chloride (BMIM-Cl), however only traces of the desired products could be observed by ^{1}H NMR. It is very likely that the silver catalyst may have been consumed by side reactions involving the formation of a carbene.[15] Further, switching from DMA to propylene carbonate in an effort to increase the solubility of carbon dioxide significantly favored the formation of the carbonate byproduct.

Alternative bases were investigated in the hopes of minimizing byproduct formation and accelerating the reaction rate. Interestingly, the use of an amine base such as Hunig's base yielded no desired product formation, nor did it appear to displace chloride. Potassium phosphate generated the desired product, but at a rate much slower than that of potassium carbonate, with starting materials still present after 18 h. Of the alternative bases investigated, potassium *t*-butoxide worked the best with yields similar to those observed when using potassium carbonate. However, owing to the more corrosive nature of this base, it was not deemed an improvement for this synthesis. Ultimately, and in accordance with Inoue's original work, potassium carbonate seems to remain the best base to be used in this system.[16]

The best conditions obtained for the unsubstituted arylnaphthalene lactone synthesis were then applied to the synthesis of a tetramethoxy-substituted arylnaphthalene lactone natural product analog (Scheme 2). The chloride precursor **5** was obtained from the 3,4-dimethoxyphenylpropargyl alcohol in 84% yield.

These new conditions were found to offer two of the four possible regioisomers in 55% yield, nearly an identical yield to that of the unsubstituted system. Only trace amounts of the minor regioisomers were observed, which is consistent with previous findings reported by Stevenson and coworkers.[4] The two major isomers, shown in Fig. 2, were formed in a 2 : 1 ratio and could be isolated as a clean mixture by simple trituration of the crude extract with ethyl acetate and hexane in



1 **2**

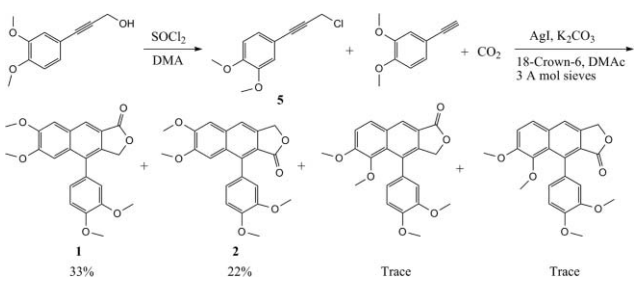
Fig. 2 Dehydrodimethylconidendrin **1** and dehydrodimethylretroconidendrin **2**.

Table 3 Performance metrics for the two syntheses

General and green chemistry metrics	Original synthesis[10,19]	Improved synthesis
%yield (for both regioisomers)	33.2	46.2
No. of steps	3	2
Solvents used	DCM, xylenes	DMA
E-factor	139.1	35.0
Atom economy (%)	73.5	73.5

43% yield. Isolation of the individual isomers, however, required chromatography.

Some green chemistry metrics were calculated for both the original approach and this new approach and are presented in Table 3.[17,18] Both regioisomers were considered as the desired product. The original synthesis was examined with the propiolate intermediate as starting point. It is important to note that the improved synthesis has the added advantage of generating this propiolic acid intermediate *in situ*, an advantage not reflected in the metrics and which eliminates an otherwise additional synthetic step.



Scheme 2 Optimized route to dehydrodimethylconidendrin **1** and dehydrodimethylretroconidendrin **2**.

These metrics compare the halogen activation, coupling, and cyclization steps used to access the desired conidendrin molecules. These steps were chosen to highlight how both syntheses share the same atom economy while requiring dramatically different resource inputs. Although the *E*-factor is still not ideal for this improved two-step synthesis, it constitutes a considerable improvement as compared to the original approach. As is commonly the case, solvent accounted for the vast majority of the waste generated by both routes.

Experimental section

Representative procedure for the silver-catalyzed one-pot synthesis of arylnaphthalene lactones 3 and 4

To a round bottom flask fitted with a condenser and a stirrer bar was introduced the catalyst AgI (23.4 mg, 0.05 mmol) under CO_2 atmosphere (1 atm). After addition of 1 mL of DMA, potassium bicarbonate (160.1 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), 3-chloro-2-phenyl-1-propyne (75 mg, 0.5 mmol), and phase transfer catalyst (0.1 mmol) the mixture was placed in an oil bath at 100 °C. After 6 h, the reaction mixture was cooled and extracted with ethyl acetate to afford a 2.5 : 1 mixture of products **3** and **4**. The products were purified by column chromatography using 1 : 5 ethyl acetate–hexane. 4-Phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**3**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 2H), 7.32 (d, 2H, *J* 7.55 Hz), 7.49 (m, 5H), 7.74 (d, 1H, *J* 7.55 Hz), 8.03 (d, 1H, *J* 6.45 Hz), 8.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.5, 123.0, 125.9, 126.4,126.7, 128.4, 129.0, 129.3, 130.1, 133.7, 134.1, 134.9, 135.8, 138.4, 171.2; *m/z* (HRMS) 261.09063 (M + H^+. $C_{18}H_{12}O_2$ requires 261.0910). 9-Phenylnaphtho[2,3-*c*]furan-1(3*H*)-one (**4**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.39 (s, 2H), 7.32 (m, 2H), 7.42 (t, 1H, *J* 7.85, 8.35 Hz), 7.47 (m, 3H), 7.58 (t, 1H, *J* 7.45 Hz), 7.74 (d, 1H, *J* 8.80 Hz), 7.84 (s, 1H), 7.90 (d, 1H, *J* 8.35 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.1, 120.2, 126.7, 128.0, 128.1, 128.3, 128.6; *m/z* (HRMS) 261.0907 (M + H^+. $C_{18}H_{12}O_2$ requires 261.0910).

Preparation of 3,4-dimethoxyphenylpropargyl chloride (5)

In a round bottom flask under 1 atm N_2, DMA (8.0 ml) and 3,4-dimethoxypenylpropargyl alcohol (490 mg, 2.55 mmol) were cooled to 0 °C in an ice bath while stirring. The thionyl chloride (0.2 ml, 2.8 mmol) was then added dropwise and the solution was allowed to slowly warm to rt over several hours. Once the reaction was complete as indicated by TLC, the mixture was quenched with H_2O, neutralized with $NaHCO_3$, extracted 3× with EtOAc, dried with Na_2SO_4, filtered and concentrated. The crude mixture was purified by column chromatography using 1 : 12 EtOAc–hexane to afford 450 mg (84%) of a yellow oil that crystallized upon cooling (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (1 H, dd, *J* 1.8, 8.3), 6.98 (1 H, d, *J* 1.8), 6.83 (1 H, d, *J* 8.3), 4.41 (2 H, s), 3.91 (3 H, s), 3.90 (3 H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.35, 149.00, 125.72, 114.86, 114.51, 111.33, 86.94, 82.77, 56.31, 56.29, 31.82; *m/z* (HRMS) 211.05187 (M + H^+. $C_{11}H_{12}ClO_2$ requires 211.052034).

Dehydrodimethylconidendrin and dehydrodimethylretroconidendrin (1 and 2)

In a round bottom tube under 1 atm of CO_2, compound **5** (105 mg, 0.5 mmol), 3,4-dimethoxyphenylacetylene (81 mg, 0.5 mmol), AgI (12 mg, 0.05 mmol), K_2CO_3 (70 mg, 0.5 mmol), 18-crown-6 (27 mg, 0.1 mmol), DMA (1.4 ml) and 3 Å mol sieves (~100 mg) were combined. The solution was then heated at 100 °C for 15 h. The mixture was then cooled, diluted with H_2O, neutralized with 1 N HCl, extracted 3× with EtOAc, washed with brine, dried with Na_2SO_4, filtered, and concentrated. 78 mg (41%) of a 2 : 1 mixture of compounds **1** and **2** could then be isolated through trituration with EtOAc, or the material could be purified by column chromatography using a 30 → 35 → 40% gradient of EtOAc–hexane to yield 63 mg (33%) of **1** and 42 mg (22%) of **2**, in addition to several mixed fractions. Dehydrodimethylconidendrin (**1**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (1 H, d, *J* 57.0), 7.19 (1 H, d, *J* 0.8), 7.05 (1 H, s), 6.98 (1 H, s), 6.91–6.87 (1 H, m), 6.83 (1 H, s), 5.17 (2 H, dd, *J* 14.9, 14.9), 3.99 (3 H, s), 3.93 (3 H, s), 3.82 (3 H, s), 3.76 (3 H, s). ^{13}C NMR (126 MHz, $CDCl_3$) 171.64, 151.96, 150.10, 149.29, 148.94, 137.91, 132.15, 131.63, 129.90, 128.61, 124.07, 121.55, 121.39, 112.16, 111.64, 107.64, 104.11, 69.56, 56.05, 56.03, 55.94, 55.86; *m/z* (HRMS) 381.13307 (M + H^+. $C_{22}H_{21}O_6$ requires 381.133265). Dehydrodimethylretroconidendrin (**2**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (1 H, s), 7.13 (1 H, s), 7.07 (1 H, s), 6.98 (1 H, d, *J* 8.2), 6.91 (1 H, d, *J* 8.1), 6.86 (1 H, s), 5.33 (2 H, s), 3.99 (3 H, s), 3.92 (3 H, s), 3.82 (4 H, d, *J* 11.4), 3.72 (3 H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.44, 152.20, 150.43, 149.28, 148.90, 140.39, 140.03, 133.59, 129.25, 127.56, 122.98, 118.74, 118.55, 113.81, 111.18, 106.40, 68.42, 60.81, 56.49, 56.38, 56.23, 56.21; *m/z* (HRMS) 381.13300 (M + H^+. $C_{22}H_{21}O_6$ requires 381.133265). NMR data for these compounds are consistent with those previously reported.[20]

Conclusions

The silver-catalyzed multicomponent synthesis of arylnaphthalene lactones was successfully applied to the preparation of compounds of the conidendrin class of lignans. This approach enables facile access to the arylnaphthalene lactone core using a multicomponent approach involving two aryl alkynes, carbon dioxide, and a silver catalyst. Unlike the previously reported multicomponent approach, these new conditions appear to be robust in their tolerance for electron-donating groups on the electrophilic component of the tandem coupling reaction, thus enabling access to the naturally occurring compounds of arylnaphthalene lactones and their analogs. In summary, this greener route is more energy and material efficient, generates less waste, and does not rely on chlorinated solvent.

Despite these advances, this approach still has several limitations in terms of green chemistry. Ideally, hazardous reagents such as thionyl chloride and 18-crown-6 would be replaced by more benign reagents. Further, although the yields were high enough to provide a viable and abbreviated route to this class of molecules, higher conversions are desirable. Future work will focus on product selectivity and will involve continued application of this methodology to explore the full scope of this approach to accessing various naturally occurring lignans.

Acknowledgements

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