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Anti-AIDS agents 83. Efficient microwave-assisted one-pot preparation of angular 2,2-dimethyl-2*H*-chromone containing compounds

Ting Zhou, Qian Shi *, Kuo Hsing Lee *

Natural Products Research Laboratories, Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina 27599-7568, USA

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ABSTRACT

A novel and efficient microwave-assisted one-pot reaction was developed to synthesize angular 2,2-dimethyl-*2H*-chromone-containing compounds, which is the first and key step in the synthesis of potent DCK and DCP anti-HIV agents. The newly developed microwave synthesis conditions dramatically shortened the reaction time from 2 days to 4 h with improved yields.

1. Introduction

Suksdorfin (**1**), isolated from Lomatium *suksdorfii*, was discovered in early 1994 to exhibit anti-HIV activity.[1] Continuing research led to the discovery of (3′*R*, 4′*R*)-(+)-*cis*-khellacone (DCK) analogs and (3′*R*, 4′*R*)-di-*O*-(−)-camphanoyl-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DCP) analogs, some of which demonstrated much more significant anti-HIV activity than **1**.[2–5] 4-MDCK (**2**) and 2-EDCP (**3**) are potent representatives of these two series and were selected as lead compounds for further modification to develop more potent and selective anti-HIV agents as possible clinical trial candidates. The skeletons of **1**, **2,** and **3** share a similar motif, a 2,2-dimethyl-2*H*-chromene (rings B and C shown in Fig. 1). Because the synthesis of the 2,2-dimethyl-2*H*-chromone motif is the first and key step in the preparation of both DCK and DCP series, the efficiency of this reaction dramatically affects the synthesis of the desired final products.

In our prior studies, the C-ring was constructed by different methods. For DCK compounds, a two-step reaction sequence involved nucleophilic substitution with 3-chloro-3-methyl-1-butyne, followed by Claisen rearrangement and cyclization in *N*,*N*-diethylaniline at a reflux temperature over 200 °C.[3] This transformation generally needed over 48 h and the yield averaged below 40%. For DCP analogs, a successful one-pot synthesis involved gradual addition of 4,4-dimethoxy-2-methyl-2-butanol into a refluxing solution of 1-(2,4-dihydroxyphenyl)ethanone in pyridine (at approximately 140 °C) to accomplish both alkylation and cyclization.[5] However, the maximum yield of the desired product still remained low (<40%) even with a 48-h reaction time. Both the conventional syntheses of 2,2-dimethyl-2*H*-chromone were not time- or yield-efficient, and partially attributable to the formation of a linear by-product (**b**-series, such as **15b** shown in Scheme 1). Therefore, for scale-up synthesis of DCK and DCP compounds, a more efficient synthetic approach was needed to shorten the reaction time, increase the yield of the desired product (**a**-series), and for better control of the formation of the linear by-product.

Microwave (MW) synthesis was considered to be a useful approach to accomplish these goals. One benefit of MW synthesis is to manage the desired reaction under appropriate conditions (time, temperature, and pressure) to achieve the desired product in a reasonably high yield. In this Letter, we report herein our recent study to design and conduct MW synthesis with varying reaction duration, temperature, and reagent, in order to optimize the synthesis of angular 2,2-dimethyl-2*H*-chromenes (**a**-series), as the key and desired intermediates in the synthesis of DCK and DCP analogs.

2. Results

In our previous Letter, the 2,2-dimethyl-2*H*-chromene **15a** in Scheme 1 was synthesized by the reaction of 1-(2,4-dihydroxyphenyl)ethanone with 4,4-dimethoxy-2-methyl-2-butanol in pyridine. The best reported yield of **15a** by this conventional method was 38% with a reaction temperature of 140 °C and a reaction time of 48 h. However, the by-product **15b** was also obtained in 6.4% yield under these conditions (Scheme 1). A possible mechanism

* Corresponding authors. Tel.: +1 919 843 6325; fax: +1 919 966 3893 (Q.S.); tel.: +1 919 962 0066; fax: +1 919 966 3893 (K.H.L.).
E-mail addresses: qshi1@email.unc.edu (Q. Shi), khlee@unc.edu (K.H. Lee).

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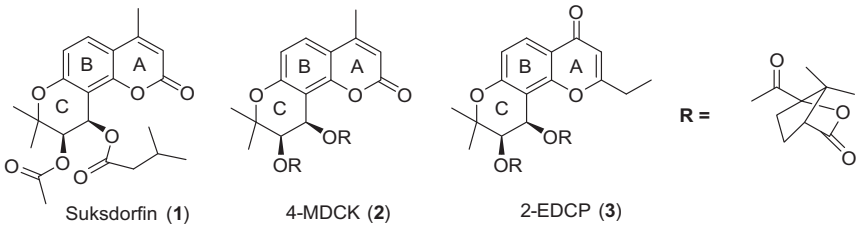
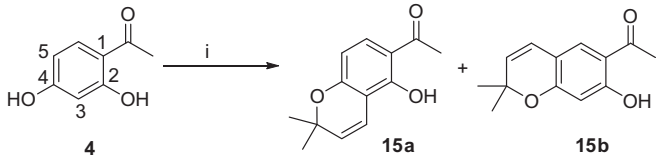


Figure 1. Structures of Suksdorfin (**1**), 4-MDCK (**2**) and 2-EDCP (**3**).



Scheme 1. Synthesis of **15a**,**b**. Reagents and conditions: (i) 4,4-dimethoxy-2-methyl-2-butanol, pyridine, microwave condition.

is proposed in Scheme 2, which illustrates the formation of the desired angular product **15a** and the undesired by-product **15b**. The activated alkylating reagent, 4,4-dimethoxy-2-methyl-2-butanol, initially attacks at the electron-rich position-3 or -5 of the starting ethanone. Subsequently, cyclization occurs between the lone-pair electrons of the ketone at position-4 and the electrophilic carbon of the butene, and CH_3OH is lost to form the angular (**a**-series from position-3 attack) or linear (**b**-series from position-5 attack) product. Using the same reagent, experiments were designed and conducted using MW initiation to find better conditions to selectively produce **15a**. The results are listed in Table 1. The reaction temperature was varied from 140 to 240 °C with 20 °C intervals, and the reaction duration was extended from 2 to 8 h with 2-h intervals. At a set reaction time, the yields of both **15a** and **15b** increased at higher temperatures, but reached a maximum at 220 °C. At this reaction temperature, the highest yield (57.4%) of the desired **15a** occurred at a reaction duration of 4 h. Although the yield of the undesired **15b** also increased slightly (6.40% vs 7.32%) under these conditions (220 °C/4 h), the MW synthesis was still a significant improvement compared with the best reported conventional reaction conditions (57.4% vs 38% yield of **15a**, respectively).

Table 1
Yields of **15a** and **15b** under varied microwave conditions

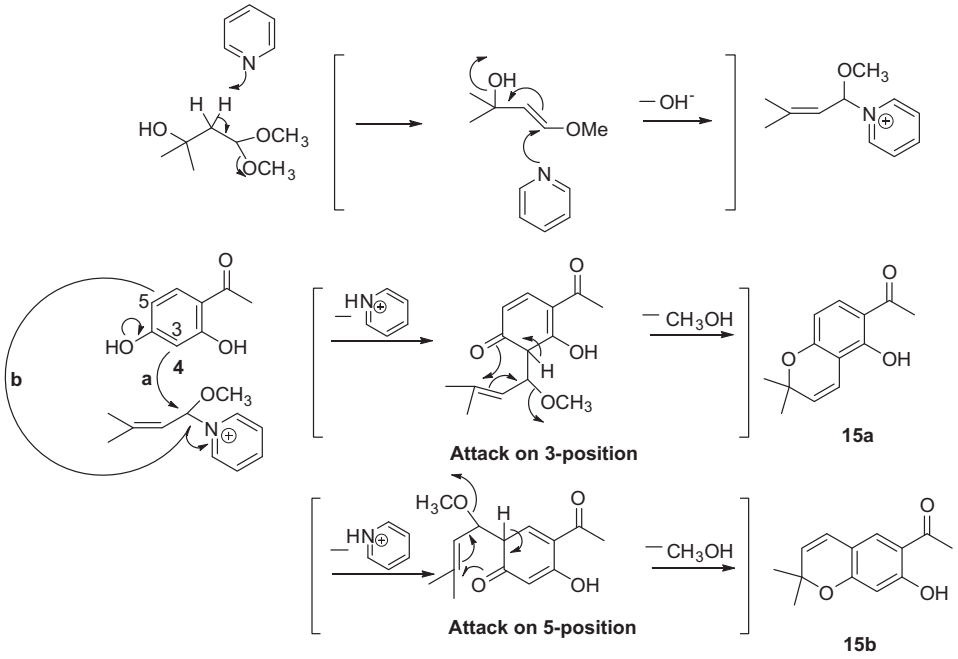
Temperature (°C)	Yield of **15a** (%)				Yield of **15b** (%)			
	2 h	4 h	6 h	8 h	2 h	4 h	6 h	8 h
140	—[a]	3.38	—[a]	—[a]	—[a]	0.49	—[a]	—[a]
160	—[a]	15.2	23.1	23.8	—[a]	1.40	2.33	2.47
180	—[a]	35.5	41.5	41.9	—[a]	4.11	5.02	7.76
200	—[a]	45.7	49.3	54.0	—[a]	6.06	6.27	7.14
220	52.7	57.4	54.0	—[a]	6.4	7.32	8.05	—[a]
240	—[a]	38.0	35.8	—[a]	—[a]	5.92	5.60	—[a]

[a] Reaction not performed.

Table 2
Yields of **21a** and **21b** under varied microwave conditions

Temperature (°C)	Yield of **21a** (%)		Yield of **21b** (%)	
	4 h	6 h	4 h	6 h
180	38.4	44.8	2.94	2.14
200	49.7	—[a]	3.62	—[a]
220	55.7	—[a]	4.08	—[a]
240	52.6	—[a]	4.58	—[a]

[a] Reaction not performed.



Scheme 2. Possible mechanism for observed transformations.

Table 3
Application of optimized microwave conditions (220 °C, 4 h) with diverse starting materials[9,10]

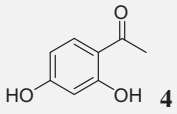
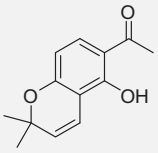
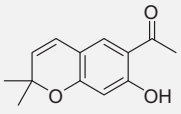
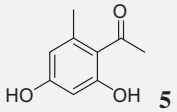
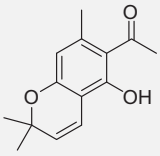
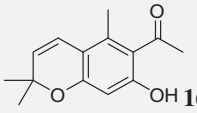
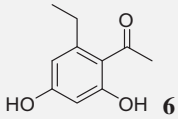
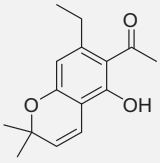
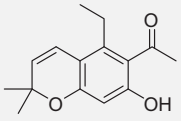
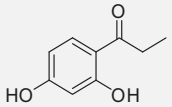
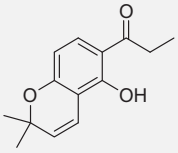
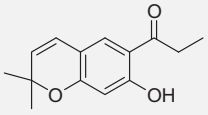
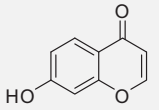
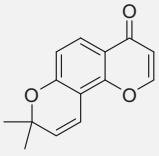
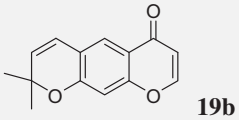
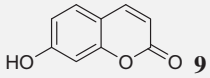
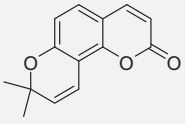
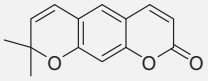
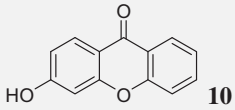
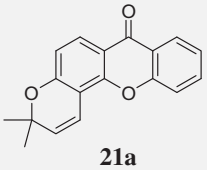
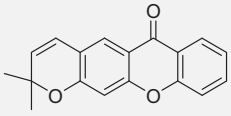
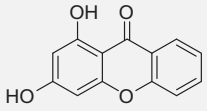
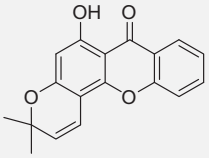
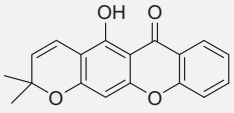
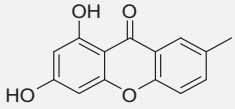
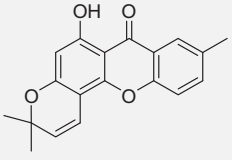
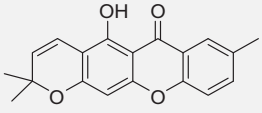
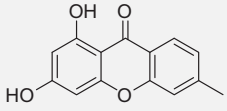
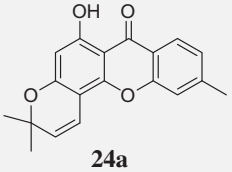
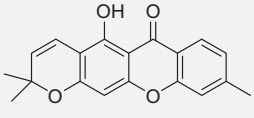
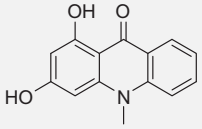
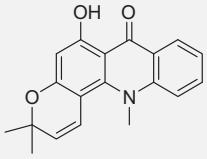
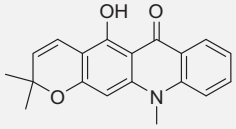
Entry	Starting material	Angular product **a**	Linear product **b**	Yield of **a**	Yield of **b**
1	 **4**	 **15a**	 **15b**	57.4	7.32
2	 **5**	 **16a**	 **16b**	66.4	9.54
3	 **6**	 **17a**	 **17b**	72.6	N/A
4	 **7**	 **18a**	 **18b**	63.5	2.65
5	 **8**	 **19a**	 **19b**	40.3	N/A
6	 **9**	 **20a**	 **20b**	31.6	5.47
7	 **10**	 **21a**	 **21b**	55.7	4.08
8	 **11**	 **22a**	 **22b**	38.9	27.2
9	 **12**	 **23a**	 **23b**	42.6	17.4
10	 **13**	 **24a**	 **24b**	38.1	7.05

Table 3 (*continued*)

Entry	Starting material	Angular product **a**	Linear product **b**	Yield of **a**	Yield of **b**
11	 **14**	 **25a**	 **25b**	36.2	4.33

To verify the optimized MW conditions, a second series of reactions were conducted using 3-hydroxy-9*H*-xanthane-9-one (**10**) as the starting material to make the corresponding tetracyclic product (**21a**). The reaction temperatures, times, and yields are listed in Table 2. The best yield (55.7%) of the desired product **21a** was again reached at 220 °C for 4 h, and was about 10 times better than the yield obtained from the conventional method with the same alkylating reagent (4.34%, Table 4, entry 7), suggesting that 220 °C/4 h may be widely applicable to efficiently produce different dimethylchromene-related products including 8,8-dimethyl-8*H*-pyrano[2,3-*f*]chromenes, 3,3-dimethyl-pyrano[2,3-*c*]xanthen-7(3*H*)-ones, or other compounds, such as 3,3,12-trimethyl-3*H*-pyrano[2,3-*c*]acridin-7(12*H*)-one.

Next, different substances containing a phenolic ring were reacted with 4,4-dimethoxy-2-methyl-2-butanol under the optimized MW conditions. The results are listed in Table 3. Most reactions generated two new products, the desired angular **a**-product and an undesired linear **b**-product, plus differing amounts of the recovered starting materials. The exceptions were entries 3 and 5 (Table 3), in which only the desired **a**-products were observed by TLC and MS. In all cases, the desired angular **a**-products were formed predominantly compared with the undesired linear **b**-products, implying that the MW reaction conditions are efficient and applicable to the synthesis of diverse dimethylchromene-related products. The **a-** and **b-**products could be separated by silica gel chromatography and identified by NMR spectroscopy.

Adding a methyl or ethyl group at the 6-position of 1-(2,4-dihydroxyphenyl)ethanone (Table 3, entries 1–3) generated better yields of the desired products [57.4% **15a** (6-H), 66.4% **16a** (6-CH_3), 72.6% **17a** (6-CH_2CH_3)]. Although the yield of the undesired **16b** was slightly higher than that of **15b**, interestingly, the undesired **17b** was not detected under the applied reaction conditions. With approximately 25% of the starting material **6** recovered, this result suggested a stereo-favorable cyclization toward the 3-position. With 1-(2,4-dihydroxyphenyl)propan-1-one (**7**) as the starting material (Table 3, entry 4), the desired **18a** was obtained in 63.5% yield, which was 6% higher than the yield of **15a** from 1-(2,4-dihydroxyphenyl)ethanone (**4**) (Table 3, entry 1). In addition, the undesired **18b** was obtained in 5% lower yield than the undesired product **15b**, leading to a much higher ratio of desired/undesired product. Both bi- (**8**, **9**) or tri-cyclic (**10**–**14**) compounds (Table 3, entries 5–10) were also treated with 4,4-dimethoxy-2-methyl-2-butanol under the established MW reaction conditions. The yields of the desired **a**-products were generally lower (31.6–55.7%, Table 3, entries 5–11) relative to those obtained with single ring reactants (57.4–72.6%, Table 3, entries 1–4). However, they were much higher than those obtained with conventional reaction conditions utilizing the same alkylating reagent. For example, the yields of the desired products **19a, 20a**, and **21a** were only 13.5%, 23.9%, and 4.34%, respectively, with conventional synthesis but 40.3%, 31.6%, and 55.7% with MW synthesis (Table 4). Unexpectedly, **19b** was not detected under either set of reaction conditions; however, the yields of **19a** were not comparably high, and the starting material **8** was mainly recovered. Compound **22a** was prepared previously by the reaction of 1,3-dihydroxy-xanthen-9-one (**11**) with 2-chloro-2-methylbutyne. After a two-step reaction sequence, the desired product was obtained in a low yield of 12.5% (Table 4).[6] Under the MW conditions, the yield of **22a** increased to 38.9%. A substantial quantity of **22b** by-product was also obtained (27.2%), suggesting that the *meta*-hydroxy group may play a role in assisting the formation of the linear **b**-type compound. Compounds **12** and **13** with a methyl substituent at the 6- or 7-position yielded lower amounts of **b**-products (**23b** and **24b**) relative to **22b**, although the yields of the desired **a**-products (**23a** and **24a**) were not significantly changed compared with **22a**. Compound **25a** was synthesized previously from 2-methyl-3-butyn-2-ol through either two- or multiple-step reactions, in a total yield of less than 20% (Table 4).[7,8] Under the optimized MW conditions, we successfully synthesized **25a** from 3-hydroxy-10-methylacridin-9(10*H*)-one (**14**) in an improved yield of 36.2%.

3. Discussion and conclusions

In this research, we were able to successfully utilize a microwave initiation method to synthesize the desired angular 2,2-dimethyl-2*H*-chromenes that are the key intermediates in the syntheses of anti-HIV DCP and DCK analogs. Through alkylation and cyclization between an appropriate starting compound and

Table 4
Comparisons of conventional and microwave syntheses

Entry no. in Table 3/Products	Conventional heating system (140 °C/48 h for entries 1, 5–7)[a] (%)		MW condition (220 °C/4 h)[a] (%)	
	Angular product **a**	Linear product **b**	Angular product **a**	Linear product **b**
1/**15**	38.0	6.40	57.4	7.32
5/**19**	13.6	N/A	40.3	N/A
6/**20**	23.9	2.55	31.6	5.47
7/**21**	4.34	1.20	55.7	4.08
8/**22**[6,b]	12.5	6.30	38.9	27.2
14/**25**[7,c]	20	—[d]	36.2	4.33

[a] Alkylating reagent: 2,2-dimethoxy-2-methyl-2-butanol.
[b] Alkylating reagent: 2-chloro-2-methylbutyne, two-step reaction.
[c] Alkylating reagent: 2-methyl-3-butyn-2-ol, two-step reaction.
[d] Not available in the reference.

alkylating reagent, a series of the desired 2,2-dimethyl-2*H*-chromene products, including 8,8-dimethyl-8*H*-pyrano[2,3-*f*]chromenes, 3,3-dimethyl-pyrano[2,3-*c*]xanthen-7(3*H*)-ones, and other products, such as 3,3,12-trimethyl-3*H*-pyrano[2,3-*c*]acridin-7(12*H*)-one, were obtained in a one-pot reaction. Compared to the literature-reported methods, the newly developed microwave-assisted conditions dramatically shortened the reaction time from 2 days to 4 h with much higher to comparable yields. Increasing the reaction temperature from 140 to 220 °C and extending the reaction time favored the formation of both **a-** and **b-**products; however, with a lower fold increase in the undesired **b**-product. Although the yields of the desired products are still not ideal, the current optimized MW conditions significantly improve selective synthesis of the desired products in comparison to the literature reports with conventional heating conditions.

We also analyzed the factors that might affect yield and regioselectivity in this reaction. The reaction yield and the regioselectivity were influenced by electronic effects on the phenolic ring. Electron-donating groups, such as alkyl groups at the 6-postion of 1-(2,4-dihydroxyphenyl)ethanone, should increase the electron density at the 3-position, which consequently enhanced alkylation reactivity at this position and the relative percentage of the desired **a**-product. In contrast, a lone electron-pair on a hydroxy group introduced at the 1-position of xanthenone (Table 3, entries 8-10) results in higher electron density at the 2-position and, therefore, reduced the regioselectivity between **a-** and **b**-products. In addition, steric effects of ring substituents may also play a role in the alkylation and cyclization. Introducing an ethyl group at the 6-postion (**6**, Table 3, entry 3) blocked alkylation from occurring at the 5-position, which led exclusively to the desired product **17a**.

This study demonstrates a significant advancement because this MW method, under optimized conditions, can be widely utilized with diverse ring systems, including phenone, chromenone, xanthenone, and acridinone. Therefore, this synthetic methodology dramatically broadens the possibility of efficiently exploring structurally diverse DCK and DCP analogs as novel anti-HIV agents. This work is currently ongoing in the authors' laboratories, and the results will be reported shortly.

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9. Sample procedure for microwave-assisted synthesis of 2,2-dimethyl-2*H*-Chromones. Synthesis of **16a** and **16b** (Table 3, entry 2): 2′,4′-Dihydroxy-6′-methyl-acetophenone (**5**) (200.0 mg, 1.20 mmol), 4,4-dimethoxy-2-methyl-2-butanol (0.37 mL, 2.40 mmoL), and anhydrous pyridine (2 mL) were added into 2–5 mL microwave vial and sealed. After pre-stirring for 20 s, the reaction temperature was increased to 220 °C for 4 h under high microwave absorption condition. At completion, the reaction mixture was cooled to room temperature, diluted with EtOAc and washed separately with aqueous HCl (10%) and brine. The organic layer was collected and the solvent was removed under vacuum. The residue was purified by column chromatography (hexanes/EtOAc = 97:3) to afford **16a** in 66.4% yield and **16b** in 9.54% yield. Compound **16a**: MS (ESI+) *m/z* (%) 233 (M^++1, 100); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.69 (1H, d, *J* = 9.9 Hz, H-4), 6.19 (1H, s, H-8), 5.52 (1H, d, *J* = 9.9 Hz, H-3), 3.31 (3H, s, $COCH_3$-6), 2.53 (3H, s, CH_3-7), 1.43 (6H, s, CH_3-2,2). Compound **16b**: MS (ESI+) *m/z* (%) 233 (M^++1, 100); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 6.52 (1H, d, *J* = 10.2 Hz, H-4), 6.27 (1H, s, H-8), 5.65 (1H, d, *J* = 10.2 Hz, H-3), 2.60 (3H, s, $COCH_3$-6), 2.49 (3H, s, CH_3-5), 1.42 (6H, s, CH_3-2,2).
10. Microwave initiator utilized to synthesize 2*H*-chromones (**15**–**25**) is Biotage initiator (300 W).