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The synthesis of indanones related to combretastatin A-4 via microwave-assisted Nazarov cyclization of chalcones

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Abstract—A fast and efficient microwave-assisted synthesis of combretastatin A-4-like indanones has been developed. Microwave irradiation provides a useful alternative to traditional heating techniques to promote the TFA-catalyzed Nazarov cyclization of chalcones.

As part of a program investigating the tubulin binding properties of combretastatin A-4 **1**[1] (CA-4) and related analogs,[2] we had need for a rapid method for the preparation of indanones. We have found that the α-methyl chalcone **2** has biological activities comparable, and in some cases superior, to those of CA-4 **1** and colchicine **3** (Fig. 1).[3] These compounds bind strongly to α,β-tubulin, causing microtubules to depolymerize, which in turn causes arrest at the G_2/M stage of the cell cycle.[4] The compounds cause selective damage to tumor vasculature, an effect that is related to their tubulin binding properties.[5,6] Compounds such as these that target tumor vasculature clearly have significant clinical promise for the treatment of cancer.[7] Our research has shown that the *s*-trans conformation of the chalcone **2** has proven to be important to its biological activity.[2a] Therefore we initiated a study of conformationally constrained analogs that mimic this *s*-trans arrangement. We have recently described the synthesis and biological properties of combretastatin-like flavones[8] and we next concentrated our attention on indanones. Indanones **4** represent a class of analogs in which the β-carbon of its corresponding chalcone is attached directly to C-2 of the A-ring. This will provide a series of conformationally constrained chalcone analogs incorporating a five-membered ring. Being chiral, the indanones will also serve as stereochemical probes for studying the colchicine-binding site of tubulin. In this letter, we describe a convenient synthesis of CA-4-like indanones.

The indanone scaffold can be constructed from chalcones by way of the Nazarov cyclization.[9,10] This

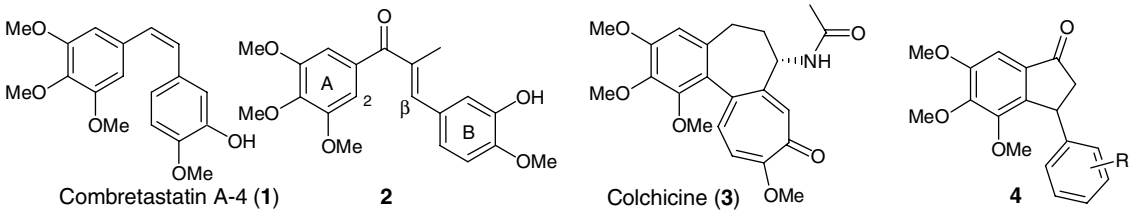

Figure 1. Structure of tubulin-binding agents.

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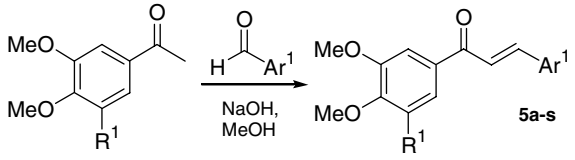
is convenient since chalcones are themselves easy to prepare and we already had a large number in hand.[11] The conventional method for the preparation of indanones involves heating a precursor chalcone in a strong acid, such as TFA, at high temperatures (120–130 °C) for extended periods of time (4–24 h).[12] We were intrigued to see whether microwave heating would significantly shorten the reaction time and thereby provide a convenient process for the preparation of CA-4-like indanones. The use of microwave irradiation is now widely adopted in organic synthesis and the drug discovery process as an alternative to traditional heating techniques. The process often results in higher yields and purer products as well as significantly shorter reaction times,[13] and is more energy efficient than conventional heating.[14]

The precursor chalcones (**5a**–**s**) were synthesized in the usual way by the NaOH-catalyzed Claisen–Schmidt condensation of appropriate acetophenones and benzaldehydes (Scheme 1).[2a] The yields of these chalcones (**5a**–**s**) are shown in Table 1. Inspection of the ^{1}H NMR spectra of the chalcones indicated that they were all geometrically pure (*E*)-isomers as evident from the alkene ^{1}H–^{1}H coupling ($^3J_{HH}$ 15–16 Hz).

We first prepared the indanones using the technique used by Rice and co-workers.[12e] The chalcones **5a** and **5b** were dissolved in neat TFA and heated to 120–130 °C in a sealed tube for 4 h. This technique gave reasonable yields of indanones **4a** and **4b**, respectively (see Table 2, route i). The technique was then modified for microwave synthesis.



Scheme 1. Precursor chalcone synthesis.

Table 1. Yields of chalcones **5a**–**s**

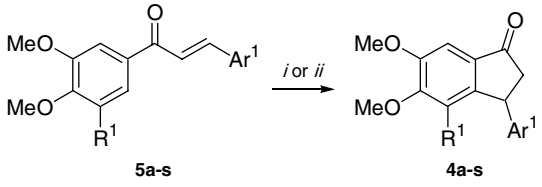
Chalcone	R^1	Ar^1	Yield (%)
5a	OMe	4-Methoxyphenyl	74
5b	OMe	3-Hydroxy-4-methoxyphenyl	69
5c	OMe	4-Chlorophenyl	55
5d	OMe	3-Bromo-4-methoxyphenyl	75
5e	OMe	3,4-Dichlorophenyl	50
5f	OMe	Benzo[*d*][1,3]dioxol-5-yl	73
5g	OMe	4-Bromophenyl	88
5h	OMe	Phenyl-4-oxyacetic acid	52
5i	OMe	2,3,4-Trimethoxyphenyl	78
5j	OMe	2,6-Dichlorophenyl	82
5k	OMe	2,4-Dichlorophenyl	83
5l	OMe	Phenyl	76
5m	OMe	3-Nitro-4-methoxyphenyl	68
5n	OMe	3-Fluoro-4-methoxyphenyl	87
5o	H	4-Methoxyphenyl	67
5p	H	4-Bromophenyl	76
5q	H	4-Chlorophenyl	76
5r	H	2,6-Dichlorophenyl	77
5s	H	3,4,5-Trimethoxyphenyl	90

Table 2. Yields of indanones **4a**–**s**

	Route	R^1	Ar^1	Yield (%)
4a	i	OMe	4-Methoxyphenyl	72
4b	i	OMe	3-Hydroxy-4-methoxyphenyl	63
4a	ii	OMe	4-Methoxyphenyl	60
4b	ii	OMe	3-Hydroxy-4-methoxyphenyl	56
4c	ii	OMe	4-Chlorophenyl	53
4d	ii	OMe	3-Bromo-4-methoxyphenyl	59
4e	ii	OMe	3,4-Dichlorophenyl	69
4f	ii	OMe	Benzo[*d*][1,3]dioxol-5-yl	54
4g	ii	OMe	4-Bromophenyl	33
4h	ii	OMe	Phenyl-4-oxyacetic acid	26
4i	ii	OMe	2,3,4-Trimethoxyphenyl	25
4j	ii	OMe	2,6-Dichlorophenyl	95
4k	ii	OMe	2,4-Dichlorophenyl	83
4l	ii	OMe	Phenyl	23
4m	ii	OMe	3-Nitro-4-methoxyphenyl	39
4n	ii	OMe	3-Fluoro-4-methoxyphenyl	37
4o	ii	H	4-Methoxyphenyl	7
4p	ii	H	4-Bromophenyl	52
4q	ii	H	4-Chlorophenyl	34
4r	ii	H	2,6-Dichlorophenyl	71
4s	ii	H	3,4,5-Trimethoxyphenyl	41

The first attempt at the microwave-assisted reaction was performed with chalcone **5a** on a 600 mg scale. The chalcone in TFA was heated at 60 °C (power 50 W) for 5 min. Analysis of the resulting mixture by TLC showed that only a small amount of the indanone **4a** had been formed. Heating at 70 °C for 10 min (100 W) also resulted in an incomplete reaction. The mixture was heated at 120 °C for 10–20 min (100 W), after which TLC revealed that the reaction was complete. The indanone was then isolated after column chromatography (SiO_2, EtOAc/hexane, 1:3) in 60% yield. These conditions proved to be sufficiently general for the synthesis of other indanones as shown in Table 2 (route ii, Scheme 2).

The TFA used in the microwave reaction should ideally be anhydrous. The synthesis of indanone **4s** using TFA as supplied was problematic. The ^{1}H NMR spectrum of the crude product showed formation of a 2.5:1 mixture of 3,4-dimethoxyacetophenone and **4s**. It appeared that the acetophenone is derived from **5s** by a water-promoted retro-Michael retro-aldol process. We dried the TFA by stirring over phosphorus pentoxide for 12 h under an atmosphere of argon followed by distillation (bp 74–5 °C/1 atm.).[15] When the reaction of **5s** was repeated with this dry TFA the product indanone **4s** was isolated in 41% yield. There was no acetophenone evident in the ^{1}H NMR spectrum of the crude reaction



Scheme 2. Reagents and conditions: (i) TFA, sealed tube, 120 °C, 4 h; (ii) TFA, μwave, 100 W, 120 °C, 20 min.

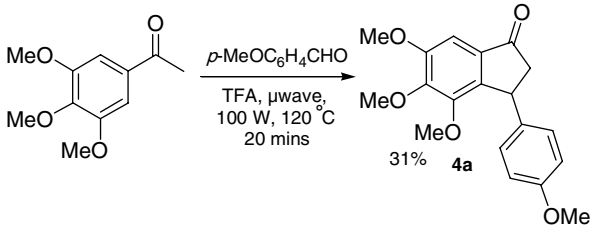
mixture. The use of the microwave reactor is ideal for handling potentially hazardous reagents such as TFA. The reactions can be performed safely: both the temperature and the pressure of the reaction vial are monitored continuously. The exposure to pressurized reaction vessels containing TFA is thereby significantly reduced.

The process conveniently provides a library of indanones possessing di- and trimethoxy substituted A-rings. The presence of the methoxy groups is highly beneficial for good tubulin-binding properties. This feature is present in many ligands that target the colchicine-binding site of β-tubulin. Acceptable yields of indanones were obtained for a variety of functional groups and substitution patterns present on the B-ring substituent.

In general, the reaction works best for electron deficient B-ring substituents. The presence of a *p*-alkoxy group is detrimental to the yield of indanone. This is consistent with the expected reactivity of the electrophilic substitution process that requires an electron-rich A-ring and electron deficient enone reaction partner. In this case, the methoxy groups of the A-ring aid the required reactivity of the chalcones as well as being necessary for good tubulin binding properties. Indeed the reaction works well for the synthesis of **4b** in which both the A and B-rings are the same as those of **1**. The indanone skeleton is an excellent scaffold for further modification. Additional substituents can easily be appended via addition to the carbonyl or alkylation at the α-carbon. The microwave-assisted Nazarov cyclization provides easy access to this important template.[12]

Since chalcones can be prepared under acid-catalyzed conditions,[16] we attempted a one-pot tandem condensation Nazarov reaction (Scheme 3). We were able to isolate the indanone **4a** but in only 31% yield. Additionally, the separation from the starting materials was not trivial, so we did not develop this further.

The cell growth inhibitory properties of selected indanones (summarized in Table 3) were determined in the K562 human chronic myelogenous leukaemia cell line using the MTT assay from a previously reported procedure.[2b] The IC_{50} value represents the concentration, which results in a 50% inhibition in cell growth after 5 days of incubation. The 3,4,5-trimethoxy substituted indanones (**4a**–**n**) generally have greater cell growth inhibitory properties than their corresponding 3,5-dimethoxy counterparts. The indanone **4b** (IC_{50} 130 nM)



Scheme 3. The one-pot Claisen–Schmidt–Nazarov-like route to indanones.

Table 3. Cell growth inhibition[a] against the K562 cell line

	IC_{50} (μM)		IC_{50} (μM)		IC_{50} (μM)
4a	0.49	**4g**	1.9	**4m**	0.08
4b	0.13	**4h**	>10	**4n**	0.1
4c	30	**4i**	2.8	**4o**	0.17
4d	1.2	**4j**	7.4	**4p**	5.4
4e	24	**4k**	2.0	**4q**	>10
4f	2.4	**4l**	>10	**4s**	34

[a] As measured by the MTT assay after 5 days of incubation of the drug with the cells cultured at 37 °C.

bearing the greatest resemblance to combretastatin A-4 displays high activity. This level of activity is potentially useful and indicates that the indanone scaffold is a framework for further design. Further details of this work will be revealed in due course.

In conclusion, we have shown that indanones can be conveniently and safely prepared by the TFA microwave-assisted Nazarov cyclization of chalcones. The indanones have been shown to possess potentially useful antiproliferative properties. Further biological effects of this library of indanones are under study and the tubulin-binding properties will be reported in due course.

General procedure for the microwave-assisted synthesis of indanones **4a**–**s**: The precursor chalcone (~250 mg) was dissolved in dry TFA (0.3 mL) and sealed in a pressure-rated reaction vial (10 mL). The reaction tube was irradiated in a self-tuning single-mode CEM Discover™ Focused Synthesiser. The reaction was maintained at 120 °C (power: 100 W) for 20 min. The mixture was then rapidly cooled to room temperature and poured into H_2O (5 mL), extracted with EtOAc (3 × 5 mL) and washed with saturated $NaHCO_3$ (aq) (2 × 3 mL). The organic extract was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, EtOAc/hexane, 1:3 to 1:1) to afford the product indanone.

Acknowledgements

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